IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

ELI LILLY AND COMPANY, : Civil No. 07-cv-3770-DMC

Plaintiff, :

v. : TRANSCRIPT OF TRIAL PROCEEDINGS

ACTIVIS ELIZABETH LLC, : VOLUME 2
GLENMARK PHARMACEUTICALS INC., USA,
SUN PHARMACEUTICAL INDUSTRIES LIMITED, :
SANDOZ INC., MYLAN PHARMACEUTICALS INC.,
APOTEX INC., AUROBINDO PHARMA LTD., :
TEVA PHARMACEUTICALS USA, INC.,
SYNTHON LABORATORIES, INC., :
ZYDUS PHARMACEUTICALS, USA, INC.,
:
Defendants.
----------x

Newark, New Jersey
May 19, 2010

BEFORE:

THE HON. DENNIS M. CAVANAUGH, U.S.D.J.

Reported by
CHARLES P. McGUIRE, C.S.R.
Official Court Reporter

Pursuant to Section 753, Title 28, United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

s/CHARLES P. McGUIRE, C.S.R.

CHARLES P. McGUIRE, C.S.R.

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THE COURT CLERK: All rise.

THE COURT: Be seated.

Good morning.

Everybody here, bright-eyed and bushy-tailed?

All right. We have our witness, Dr. Berridge, on the stand still. We were just concluding or getting close to cross-examination.

Mr. Lipsey?

MR. LIPSEY: Thank you, Your Honor. I will try to remain true to my word. I have just a few items.

C R A I G B E R R I D G E, called as a witness on behalf of the Defendants, and having been previously sworn, testified as follows:

CROSS-EXAMINATION (CONTINUED)

BY MR. LIPSEY:

Q. Dr. Berridge, when we broke, we had been debating the importance of knowing the neural methods by which drugs worked or the neural methods -- neural phenomenon that are being affected in the brain in terms of drug design. You remember that discussion?

A. Yes, sir.

Q. And I just wanted to confirm that you are the current recipient of an NIH grant in the amount of about $460,000 for the current year in order to do studies into the neural mechanisms that underlie the cognition-enhancing actions of

psychostimulants and the neural biology of higher cognitive function in order to provide information necessary for the development of new pharmacological treatments. Isn't that right?

A. Yes, sir.

Q. And as a housekeeping matter, we mentioned yesterday the Riddle 1991 article, which you had considered in preparing your opinions.

I would like --

MR. LIPSEY: If I may approach, Your Honor.

Q. -- to show you what has been marked as Plaintiff's Exhibit 636, which is the Riddle 1991 article.

And for the record, that is the Riddle 1991 article you considered in forming your opinions; correct?

A. I think it is.

Q. Okay, and in the abstract, it indicates that the labeling for desipramine relating to the sudden-death issue had been changed in 1990; correct?

A. Yes, sir.

Q. Now, if you have the volumes that you had yesterday, in Volume 3 at what's tabbed eight, there's a big fat document, which is the file history of the patent-in-suit, Plaintiff's Exhibit 2. Do you have that?

A. I have it, yes.

Q. Okay. And you did consider the file history of the

patent-in-suit in forming your opinions; correct?
A. Yes, sir, I did.
Q. And you saw very deep in the document towards the end of Examiner's Reasons For Allowance that are in there; right?
A. I'm sorry, I couldn't really hear that. What was that?
Q. One of the things you considered was the Examiner's Reasons For Allowance that appear towards the back of this large file; correct?
A. Yes.
Q. Now, in that same volume at tab seven is the actual patent-in-suit, Plaintiff's Trial Exhibit 1, and looking at the first page of it, you see the list of some of the references that are cited in that prosecution history; right?
A. I do.
Q. And among them, over there on our right-hand side is the Physicians' Desk Reference record for desipramine for 1993; right?
A. Yes.
Q. And as a matter of housekeeping, I would like to show you Plaintiff's Trial Exhibit 1296, which is a copy of the desipramine Physicians' Desk Reference for 1993, in fact, a copy right out of the file history, and that was among the

things that you considered in forming your opinions; correct?

A. It was.

Q. And if we look at the desipramine label in 1993, over on the right-hand column under "Warnings," and go down to number four, we see "Use In Children": "Norpramine-desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See Adverse Reactions, Cardiovascular." Do you see where I've read?

A. Correct.

Q. And that was one of the things you considered in forming your opinion; correct?

A. It is, yes.

MR. LIPSEY: Your Honor, I would at this point like to offer into evidence for the record the prior art, which was the -- in the contents of the binder we spent most of the time yesterday with.

THE COURT: This is binder number 3? Is that the one? Yes.

Five? Oh, five. Five.

MR. LIPSEY: I think it's four, Your Honor.

THE COURT: No, no. Five.

MR. LIPSEY: It's five.

THE COURT: Five, you said?

MR. LIPSEY: Five, I'm told.

THE COURT: Any objection?

MR. ROCKEY: No objection, Your Honor.

THE COURT: Just so we're clear, these are tabs 11 through 31.

MR. LIPSEY: Yes. For the record, I was just going to read off the exhibit numbers, if I could.

THE COURT: Okay. Go ahead.

MR. LIPSEY: That included Plaintiff's Trial Exhibits 5, 6, 621 and 635, and Defendants' Trial Exhibits 18, 20, 32, 33, 55, 59, 61, 66, 67, 93, 112, and 314.

And from this morning, I would offer in evidence the file history, Plaintiff's Trial Exhibit 2, the desipramine Physicians' Desk Reference entry, Plaintiff's Exhibit 1296, and the Riddle '91 article, Plaintiff's Exhibit 636.

MR. ROCKEY: No objection, Your Honor.

THE COURT: In evidence.

(Plaintiff's Trial Exhibits 2, 5, 6, 621, 635, 636 and 1296 and Defendants' Trial Exhibits 18, 20, 32, 55, 59, 61, 66, 67, 93, 112 and 314 marked in evidence)

MR. LIPSEY: Thank you very much for your time, Dr. Berridge.

I have no further questions at this time.

THE COURT: Any other questions of Dr. Berridge?

MR. ROCKEY: We have just a few, Your Honor.

THE COURT: All right. Well, that's redirect. Anybody else have questions before we get to redirect?

MR. PARKER: No, Your Honor.

THE COURT: Okay. Redirect.

MR. ROCKEY: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. ROCKEY:

Q. Dr. Berridge, I'd like to put up on the screen your testimony from yesterday at page 220 because I had a question about it.

Now, I'd like you to take a look at that question and answer.

THE COURT: Just so we're clear, this is his direct, or cross?

MR. ROCKEY: No, this is his cross, Your Honor.

THE COURT: Go ahead.

Q. And my question to you is, what were you saying there?

THE COURT: Well, wait. Wait a minute. I don't know if it's appropriate that we're going to allow him to start looking at his transcript from the day before's testimony and to start explaining what he said in that testimony. The testimony is what it is. If you believe that something has to be clarified or you believe something

is unclear or you want to expand upon something, certainly that's okay; but I'm not going to start going through all his testimony and having him reiterate and/or clarify.

MR. ROCKEY: No, Your Honor, that's -- let me rephrase the question. I think I can take care of it.

MR. LIPSEY: May we take the transcript down off the screen at that point?

THE COURT: Well, it's not confidential. But yes, we -- you can do what you want with that. Go ahead.

MR. ROCKEY: Thank you.

BY MR. ROCKEY:

Q. Do you distinguish, Dr. Berridge, between pharmacological action and the biology of ADHD?

A. Yes, I do.

Q. And what is the distinction that you draw in that respect?

A. Well, the pharmacological action is what the drug does in a -- well, in a pharmacological sense, which is a circular answer, I guess, but it's, what is the drug doing immediately, what is it interacting with, physically interacting with, and how does that physical interaction change some process.

So when we talk about a reuptake blocker, it blocks -- it binds the reuptake sites and it blocks those actions, the actions of those reuptake sites. That's

something that can be measured, and that's typically how drugs are described. They're described by their primary action, pharmacological action.

When we talk about the neurobiology of ADHD, you know, there, you're talking about, well, what's different in the brain of ADHD subjects? And that's something we don't know today, it's a complicated question, it's a difficult question to answer, but that's not unique to ADHD, that's common to all behavioral disorders that are treated pharmacologically.

Q. Thank you.

Now I'd like to turn to the Shenker article, which counsel showed you yesterday. That's PTX-6F, 1023 in the big notebooks.

A. Are we talking about Volume 3?

Q. Yes. I'm sorry. Volume 5.

A. I'm sorry. Three was in front of me.

THE COURT: And which tab is this?

MR. ROCKEY: This is tab 23, Your Honor.

THE COURT: Twenty-three.

Q. And I'd like to have you turn to page 340 of the Shenker paper.

A. Okay.

Q. Now, there's a reference there to the reduced efficacy of DMI and imipramine.

What is that difference in efficacy referred to there?

A. The tricyclics, including imipramine and desipramine, when you compare the magnitude or the strength of their efficacy in treating ADHD, although they're effective in improving the symptoms, the magnitude of that effectiveness is smaller than the psychostimulants.

THE COURT: Wait. Say that again. Smaller than?

THE WITNESS: Is smaller than the psychostimulants. Psychostimulants give you a larger, more robust therapeutic effect. The tricyclics give you a therapeutic effect, but when you compare the effect size, they're a little bit smaller.

Q. And what's the reason for that difference in effect?

A. No one knows.

Q. In terms of pharmacologically.

A. Well, what Shenker is pointing to, and I think this is the right interpretation, is that because stimulants -- the tricyclics don't have a large effect on dopamine reuptake blockade, but because the stimulants do -- well, so the tricyclics and the stimulants both block norepinephrine. In the case of desipramine, we know that's only norepinephrine. And what's different between desipramine and the psychostimulants is that the psychostimulants also block dopamine reuptake, increasing the levels of dopamine.

So if you ask the question, well, we know psychostimulants are more effective than tricyclics, and we know that psychostimulants do one other pharmacological action than the tricyclics, that's blocking dopamine, then what you say is that the better effects of psychostimulants probably involve the actions of dopamine in addition to the actions of norepinephrine.

Q. And what was Shenker's conclusion on that point?

A. I think that's what he concludes. Let me read this paragraph.

Yes. So that's exactly what he's saying. The reduced efficacy of imipramine and desipramine compared to the stimulants is of interest because antidepressants are less potent or much less potent at inhibiting dopamine uptake.

Q. Now, that last sentence there, desipramine may be the drug of choice; how do you interpret that?

A. Well, what they're talking about here are children with chronic tic disorders, and chronic tic disorders involve a malfunction of a brain region that is modulated by dopamine. And dopamine -- drugs that increase dopamine action tend to make the tic -- my understanding is tend to make the tic symptoms or the -- exacerbates the tic disorder. So you don't want to give children or anyone with a tic disorder a drug that increases dopamine is my

understanding.

Q. Okay.

Now I'd like to turn to page 341 of the Shenker paper. If you could take a look at that paragraph, what does that paragraph suggest to you?

A. Well, I think what they're saying is that just -- well, what they're saying is two antidepressant -- classes of drugs that are known antidepressants, the tricyclics and the monoamine oxidase inhibitors, are effective in treating depression and they've been used extensively for that, and in general, these drugs are effective in treating ADHD, there are plenty of studies that show that, but it shows that not every single drug in this antidepressant category will -- will necessarily be effective in treating ADHD, and they point out that mianserin is an atypical antidepressant and it is not effective in treating ADHD. They go on to point out, as I did yesterday, that the difference here is that mianserin also blocks alpha-2 receptors, and as I reviewed yesterday, because alpha -- drugs that stimulate alpha-2 receptors are effective in treating ADHD, it would make sense that if you block those receptors, you might reduce the effectiveness of a drug for treating ADHD.

Q. Now, yesterday, you were shown a table on page 341 -- a table on page 359, sorry.

Now, this was a prognostication, was it not?

A. Can you explain what you mean by that term in this context?

Q. Let me try again with the question.

This was a suggestion for future work; right?

A. This was a suggestion for future work for drugs that might match the efficacy level of the psychostimulants, which again are known to be more effective in general than the tricyclic antidepressants.

Q. And there are no -- in what Dr. -- or what this publication is teaching, Dr. Shenker, is, it doesn't in that table describe norepinephrine reuptake inhibitors, does it?

A. No.

MR. LIPSEY: May I?

As long as it will be a goosy-gander rule and that leading is not going to be objectionable, it is an efficient way to get it in. I just don't want to not object and then be struck down.

THE COURT: I don't strike down anyone.

(Laughter)

THE COURT: Leading, with experts, I give a lot of latitude because we can save a lot of time.

MR. LIPSEY: I understand.

THE COURT: If you think it's being overdone, if either side thinks it's being overdone, but I'll allow this. You'll be allowed the same latitude.

MR. LIPSEY: That's fine. Okay. Thank you.

MR. ROCKEY: Did we get a response to that?

THE WITNESS: Yes. Can you repeat the question?

MR. ROCKEY: Yes. Will you read it back, please?

(Record read)

A. No, right. So then my reply then is no, it does not, again, because this is his suggestion of drugs that might match the efficacy of psychostimulants, and we already knew that norepinephrine reuptake blockers alone, that that's what they did, did not match the efficacy of stimulants.

Q. Did Dr. Shenker rule out compounds which inhibit reuptake of norepinephrine altogether?

A. In this case?

Q. In this paper.

A. No.

Q. Okay. Turn to page 340, and under the heading "Tricyclic Antidepressants," does he have anything to say about the use of norepinephrine reuptake inhibitors?

A. This is the same paragraph we looked at earlier?

THE COURT: Yes.

Q. Well, look at the top paragraph under this --

A. Okay.

Q. -- the top paragraph under the "Tricyclic Antidepressants."

A. Yes. Well, this is again repeating what I've said,

which is that tricyclic antidepressants, and he includes desipramine in that list, are indirect activators of brain catecholamine receptors because they block reuptake, and they're less effective in treating -- than stimulants when you're treating ADHD.

Q. Okay. And let's go on now to Table 2 on page 342.

Now, this refers to drugs that have actually been studied, does it not?

A. This refers to drugs that have been shown -- studied in the context of treating ADHD and have been shown to -- yes, in the context of treating ADHD.

Q. And does this say anything about their relative activity?

A. Well, again, this is showing that amphetamine methylphenidate and pemoline are psychostimulants, they're just different types of psychostimulants, and we know they're very active. This monoamine oxidase inhibitor class, these he's describing as very effective, and then less effective is the tricyclics, and for those -- for that class, he specifically lists desipramine and imipramine.

Q. Okay.

A. And that, you know, is just a summary of what the clinical studies have indicated.

Q. What does that table tell you about the efficacy of desipramine?

A. That it's effective, but not as effective as the psychostimulants.

Q. And what does Dr. Shenker attribute that activity to?

A. As you see, norepinephrine uptake inhibition.

Q. Thank you.

One last point, Dr. Berridge. We saw on page 340 a reference to desipramine as a drug of choice for a certain circumstance. Does anyone else suggest the use of desipramine in the treatment of ADHD, any other literature?

A. Again, as we reviewed yesterday, there are many papers, many from the Harvard research group, but not solely, that have shown that desipramine is effective in treating ADHD, and they point out that -- we didn't talk about this yesterday, but they talk -- they point out that these drugs are effective in treating ADHD in children with a variety of comorbid disorders and one of them is tic disorders, another one would be anxiety disorders or depression.

MR. ROCKEY: Okay. Let's go on. We've got a slide here that Dr. Berridge has not seen in its present form, but let's go on to that.

Q. Now, the literature -- does the literature teach what's illustrated in this slide, namely, the TCAs's effect on norepinephrine transmission?

A. Yes.

Q. Okay. Now, you mentioned yesterday in your testimony that there were other drugs that had been used in the literature to treat ADHD, and I believe one of those was alpha-2 agonists?

A. Correct.

Q. Okay. Let's go to that.

How does clonidine affect norepinephrine reuptake inhibition?

MR. LIPSEY: Objection, Your Honor. This is precisely what I was concerned about when I asked at the beginning of my examination, you've got 40 references in your report and you talked about seven, are you done. And they said they were done and they were not relying on this clonidine theory.

MR. ROCKEY: Well, we're not relying on it, Your Honor, but Mr. Lipsey brought it up yesterday in the cross-examination. I think I'm entitled to explore the witness' testimony with respect to clonidine.

MR. LIPSEY: I showed the witness five or six publications that showed what the art believed was the mechanism of action for clonidine to show that it actually was thought to reduce norepinephrine reuptake back in the relevant time frame. That's all I did.

MR. ROCKEY: What I'm shooting for, Your Honor, is that clonidine, as the literature suggests, that affects

norepinephrine transmission. Now, we're not relying on it because we don't need to; but it does affect norepinephrine transmission, and, of course, Mr. Lipsey opened the door to clonidine when he covered it on cross.

THE COURT: Well, merely because he mentioned the word clonidine doesn't mean that everything about it might be opening the door.

But I truthfully just don't recollect the extent of the witness' testimony regarding this.

I'm going to allow it.

MR. ROCKEY: Thank you, Your Honor.

BY MR. ROCKEY:

Q. Now, another group of compounds that Mr. Lipsey asked you about yesterday, Dr. Berridge, were MAOIs, monoamine oxidase inhibitors.

What effect would they have on norepinephrine?

MR. ROCKEY: Actually, Your Honor, I think I forgot to have Dr. Berridge explain what clonidine does.

THE WITNESS: Yes. You had asked me a question, but -- then you guys chatted.

MR. ROCKEY: Yes. I got interrupted.

THE COURT: Go ahead.

Q. Go ahead.

A. Okay. So when we talk about clonidine, it's a little more -- it's a little more complicated, because clonidine is

what we call an alpha-2 agonist, it stimulates those receptors mimicking norepinephrine, and when those receptors are on that postsynaptic neuron, these neurons are talking to each other and making the brain work in the way it works. When they bind to these presynaptic alpha-2 receptors, then they reduce norepinephrine release, and that's a negative feedback mechanism to keep things operating within some optimal range. You give an alpha-2 agonist, you're going to have two parallel actions. On the one hand, you are going to suppress the release of norepinephrine, as was pointed out yesterday in my cross, and that had always been confusing. We knew psychostimulants increase norepinephrine, we knew tricyclics increase norepinephrine, and the monoamine oxidase inhibitors do the same. So you had three classes effective in ADHD that increase norepinephrine, and one that was suppressing norepinephrine. But back in the mid or late 1980's, it was discovered that many alpha-2 receptors sit postsynaptically. And then there was work by others who showed that when you stimulate these receptors postsynaptic alpha-2 receptors, you improve cognitive function that's similar in nature to cognitive function affected in ADHD. And that was the basis for our 1993 paper that was raised yesterday as well as another paper in 1994 by a woman named Coull, C-o-u-l-l, suggesting that stimulating these postsynaptic alpha-2 receptors can

improve cognitive function, and that's probably relevant to their use in the treatment of ADHD. So that explanation seemed to clarify what had always been confusing to the literature. And this postsynaptic alpha-2 receptor, the fact that it exists, the fact that it's relevant to ADHD, that took a while to percolate out of the basic neuroscience literature into the clinical literature.

Q. Okay. You also were asked yesterday by Mr. Lipsey about psychostimulants. I'm sorry, we were going back to MAOI.

Would you explain how, if at all, MAOIs affect norepinephrine transmission?

A. They do affect norepinephrine transmission. They also affect serotonin transmission and dopamine transmission. And the way they do that is, after the transmitter is taken back up through these reuptake sites, this enzyme, monoamine oxidase, degrades some portion of what's been taken up. If you block that action, as these monoamine oxidase inhibitors do, you have more neurotransmitter for release, and we know that that then leads to higher levels of transmitters, or the theory has always been that that leads to higher levels of neurotransmitters out in that synaptic area.

Q. Now, the last category that you were asked about were psychostimulants. Do they affect norepinephrine reuptake transmission?

A. As I've mentioned earlier, they block both dopamine and norepinephrine reuptake inhibition, and that's pretty much all that they do outside in this area. At high doses, amphetamine also blocks monoamine oxidase, and that's where some of the theories about why you need a drug to get taken up and block monoamine oxidase. But methylphenidate doesn't do that or Ritalin doesn't do that, so that doesn't seem to be a requirement.

Q. If we look at all of these drugs together that have had an effect on norepinephrine transmission, what do we see?

A. Well, --

MR. LIPSEY: Objection, Your Honor. This is now the grand hypothesis that was supported with the 40 references. They relied on desipramine in their case-in-chief. I object.

THE COURT: Well, wait. Wait. Explain that again.

MR. LIPSEY: He had a very complicated theory in his report where he synthesized the entirety of the literature and looked at this drug and that drug and the other drug, and he had 40 references that supported it, and I was surprised when I came in and all of a sudden there were seven references and all they were relying on was desipramine. That was the testimony. And so I asked, is

that it? And I was told yes. And now on redirect examination, now, the grand 40-reference theory is being brought into evidence, relying now on some kind of suggestion from four categories of drugs. And I think that's unfair, and I object.

MR. ROCKEY: Your Honor, the purpose of this all is to simply show that all roads lead to norepinephrine. The Plaintiff has suggested that this norepinephrine theory really has no foundation, and our point is simply to suggest that when you consider all of the literature and all the ADHD treatments that counsel brought up in cross-examination yesterday, they have one thing in common: They all affect norepinephrine transmission. And that demonstrates the importance of norepinephrine transmission and rebuts the attempt by Lilly to suggest that nobody pays any attention to norepinephrine transmission any more. That's the point. We're not relying on these other references. We're still hanging our hat on desipramine, and we've not changed theories at all. What we're doing is responding to the arguments Lilly has made.

THE COURT: Do you agree with counsel's statement that he just made that all of these things are considered?

THE WITNESS: All of these things are considered in -- relation to something specific?

THE COURT: Well, as he just stated.

THE WITNESS: I -- I agree. I could -- I would make a first point.

THE COURT: What's that?

THE WITNESS: The first point is that you don't need all treatments, known treatments to work through a common mechanism. We know that's true for lots of disorders. You can treat it with different types of treatments. Hypertension can be treated by beta agonists, alpha-1 antagonists, calcium channel blockers. It doesn't puzzle us that different modes of treatment would commonly affect some disregulated system. So I don't think you need to have all treatments have the same action, and drug discovery programs have never relied on that. Depression is treated by norepinephrine and serotonin reuptake blockers. It's also treated by serotonin reuptake blockers. And we've always used the previous drugs as the model, and from that perspective, desipramine is a good model. But if you want to say all these treatments don't have -- if you want to say do these treatments have something in common, they do, and the one thing is they increase norepinephrine neurotransmission. I'm not sure that's -- you know, relevant to the argument that desipramine's a good model.

THE COURT: Anything further?

MR. ROCKEY: No, Your Honor.

THE COURT: Any other questions on other subjects?

MR. ROCKEY: No, Your Honor.

THE COURT: Any recross?

MR. LIPSEY: I do have just a couple of points, if I may.

If we could have that demonstrative exhibit that was up on the board back.

THE COURT: Which one?

MR. LIPSEY: The last one.

MR. ROCKEY: The last one?

MR. LIPSEY: The last one.

MR. ROCKEY: You want all four?

MR. LIPSEY: All four.

RECROSS EXAMINATION

BY MR. LIPSEY:

Q. Without waiving my objection, your counsel has drawn your attention to the actions of desipramine, clonidine, MAOIs, and psychostimulants; correct?

A. Correct.

Q. And pharmacologically, every one of those molecules does something more than simply block norepinephrine reuptake; correct?

A. Absolutely.

Q. Okay. And referring to this question of postsynaptic alpha-2 receptors, the clonidine work in context of ADHD with postsynaptic receptors in mind really didn't hit the

literature until starting around 1995-'96; correct?
A. The first clinical studies talking about that were in 1995-1996. There was this 1994 paper by Coull that raised this idea. We refer to it in our 1993 paper. There was a neuroscience abstract, which is a publication, that was in 1994, I believe, with a specific mention of the use of postsynaptic alpha-2 agonists in treating ADHD. That was by authors that eventually went on to publish that first 1996 study with the postsynaptic preferring alpha-2 agonists.
Q. Do you have your deposition there, which I believe was in volume 2, starting at page 79, line 24.
A. I have to find the volume.
THE COURT: Page 79?
MR. LIPSEY: I'm sorry. Page 79, line 19. It will extend over onto 80.
Q. You were asked the following question --
THE COURT: Wait just one second.
Do you have it in front of you?
THE WITNESS: Line 19. Yes.
Q. You were asked the following question and gave the following answer:
"QUESTION: Well, you say you don't recall, but it certainly would have stuck in your mind if you had come across an article which said precisely your observation, right, Doctor? Wouldn't that have jumped out at you?

"ANSWER: Well, what jumped out at me was that there were a number of papers that are talking about norepinephrine. As we talked about, the clonidine work in the context of ADHD, with postsynaptic receptors in mind, really didn't hit the literature until starting right around 1995, 1996."

A. Correct.

Q. "Like I said, Amy -- " -- referring to Dr. Amy Arnsten (ph) -- " -- has a published an tract in '94. She has a review article along those lines in '96, which I know was submit earlier than '96, but, you know, it was just getting into the literature about that time. So it's not surprising to me that maybe postsynaptic alpha-2 receptors weren't part of the discussion."

That was testimony at that time; correct?

A. Yes.

MR. ROCKEY: Objection, Your Honor.

THE COURT: What's the objection?

MR. ROCKEY: Improper impeachment.

THE COURT: Why is that?

MR. ROCKEY: Because this statement is not inconsistent with what he said.

THE COURT: Well, that's always an issue with respect to impeachment.

It certainly clarifies, so I'm going to allow it.

I think it's a little bit different -- not different so much, but I think it supports the position of the question. So I'll allow that.

Go ahead.

MR. ROCKEY: Thank you, Your Honor.

BY MR. LIPSEY:

Q. Now, if we could go back to the Shenker article, please, which is tab 23, Plaintiff's Trial Exhibit 6, and it's on page 342, if we could have Table 2, to which you were directed.

Now, you made reference to the column on the right-hand side in which desipramine and imipramine were described as norepinephrine uptake inhibitors; right?

A. Correct.

Q. And the heading in that column is "Proposed Major Mechanism of Action"; correct?

A. Correct.

Q. So even in 1992, when Dr. Shenker is writing this article, that is deemed to be the proposed major mechanism of action; correct?

A. Consistent with the articles we reviewed yesterday which cite that as the primary mechanism, correct.

Q. "Proposed Major Mechanism of Action," correct? That's what it said.

A. That's what this title said.

Q. And if you turn to page 355 of Shenker, Plaintiff's Trial Exhibit 6, under the heading "Interaction of Dopaminergic and Adrenergic Systems," if we could have the first paragraph, Dr. Shenker wrote there: "For the purposes of clarity, the effects of drugs on brain receptors for dopamine, norepinephrine and epinephrine have been discussed in separate sections - this is a gross oversimplification as far as their effects on the operation of the brain are concerned. As mentioned, a drug is classified according to the site for which it has highest affinity, but, depending on dose, it may be able to interact with receptors or uptake sites for several different neurotransmitters. Furthermore, even highly selective agonist and antagonists can elicit effects on other neurotransmitter systems because of functional interconnections."

Do you see where I've read?

A. Yes.

Q. And you agree with that; correct?

A. There are two issues being raised.

Q. Do you agree with the statement that Dr. Shenker made?

A. Yes.

MR. LIPSEY: Thank you. We have no further questions.

THE COURT: Anything further?

MR. ROCKEY: No, Your Honor.

THE COURT: All right. Doctor, thank you very much.

THE WITNESS: Thank you.

THE COURT: You may step down, sir.

MR. ROCKEY: I wonder if Dr. Berridge would explain something that he was -- on that last quotation from Dr. Shenker's paper. I'd like to give him that explanation, Your Honor -- or give him the opportunity to offer that explanation.

THE COURT: Was there something unclear or was there something further necessary to your answer to Mr. Lipsey that you didn't get a chance to say?

THE WITNESS: I think that there was something relevant to make a point, yes.

THE COURT: And what is that?

THE WITNESS: There really were two statements. The first one was, we classify a drug by its primary pharmacological action, but that drug could have multiple actions, and we've already agreed that tricyclics do that, they block the reuptake is considered the primary action, the receptor actions are linked to other effects.

The second point was that even a highly selective drug can then change other transmitter systems. That's that circuitry issue, and I don't think it's relevant when we're identifying drugs that might be -- when we do a drug

discovery analysis of what might be a useful compound, that's -- after you do your receptor or reuptake site, how does that then change to brain. And that's going to involve one neuron talking to another to another to another and you're changing that line of communication. And that's what we never understood how these drugs work, these drugs or any drug that affects behavior.

THE COURT: Anything further?

MR. ROCKEY: That's it, Your Honor.

MR. LIPSEY: Nothing further, Your Honor. Thank you.

THE COURT: Thank you. You may step down.

(Witness excused)

THE COURT: Next witness.

MR. CLEMENT: Just one minute, Your Honor.

Your Honor, Defendants call Mr. John Goolkasian to the stand.

MR. LIPSEY: Your Honor, from our side, my partner, Mr. Burwell, will be responsible for the witness.

THE COURT: Okay.

Could we also, maybe, if we're not going to be using those books that Dr. Berridge had, just move them away? Only because there's not a lot of room up there and we'll be crowding our witnesses.

MR. CLEMENT: And we have new books to bring up.

THE COURT: I figured you might.

THE COURT CLERK: Placing your left hand on the bible, raising your right hand:

J O H N T. G O O L K A S I A N, called as a witness on behalf of the Defendants, and having been duly sworn, testified as follows:

THE COURT CLERK: Please be seated.

Please state your name, spelling it for the record.

THE WITNESS: My name is John T. Goolkasian, that's G-o-o-l-k-a-s-i-a-n.

THE COURT: Could I get that spelling again? Your name, spelling, again?

THE WITNESS: G-o-o-l-k-a-s-i-a-n.

Your Honor, I should explain, I'm deaf in this left ear, completely deaf, and hearing aids won't help. So if you say something and I miss it, I'll try to get it.

THE COURT: Okay. Are you having any difficulty -- well, let's see if you have any difficulty.

If you need to move -- if you want to move the other podium over here closer, that's fine with me.

And, counsel, if someone can't hear, you may move up, I mean, if you need to, if he's in your way.

MR. LIPSEY: I was just wondering if it's possible to raise the volume on the microphone.

THE COURT: The only problem with that -- we can try it, but as you heard before --

MR. LIPSEY: Oh, we got the feedback.

THE COURT: This is another system that we spent about four or $500,000 on --

(Laughter)

THE COURT: -- and what it does it, it rings. It just all-around annoys me.

MR. LIPSEY: Okay. Okay. Fair enough.

THE COURT: But we can try it.

If you have any difficulty hearing, let me know, sir.

MR. CLEMENT: Mr. Goolkasian, are you going to be okay?

THE WITNESS: Yes.

MR. CLEMENT: I just have some witness binder books.

DIRECT EXAMINATION

BY MR. CLEMENT:

Q. Mr. Goolkasian, are you currently employed?

A. Yes, I am. I'm a --

Q. What is the nature of your current employment?

A. I'm a self-employed attorney, working primarily as a consultant and expert witness.

Q. In any particular areas?

A. Yes. I work in a lot of drug cases, work in the electrical area and mechanical cases, especially medical devices.

Q. Are you a patent attorney?

A. Yes, I am.

Q. How long have you been a practicing patent attorney?

A. I've been a practicing patent attorney since 1969.

Q. And do you have a technical background?

A. Yes.

Q. What is that technical background?

A. I have a degree in chemical engineering from Northeastern University in 1956.

Q. And have you been employed at the Patent Office?

A. Yes, I've been at the Patent Office for 24 and a half years at virtually all levels of the office, up to the Board of Appeals.

Q. Okay. What positions did you hold at the Patent Office?

MR. BURWELL: Your Honor, in order to expedite the proceedings, we would be willing to stipulate to Mr. Goolkasian's qualifications to testify as a Patent Office practice expert.

MR. CLEMENT: We would like to offer him both as a Patent Office practice expert and on duty of candor.

MR. BURWELL: We will stipulate to offering him as

an expert on the duty of candor as it applied during that prosecution.

MR. CLEMENT: Okay. That's fine, Your Honor.

THE COURT: Okay.

MR. CLEMENT: I do just want to go over a couple other qualifications, however.

THE COURT: All right.

MR. CLEMENT: I think they're pertinent.

BY MR. CLEMENT:

Q. Mr. Goolkasian, did you ever work on the Inter-Partes -- let me just see if I can find it -- did you ever work as a protest and Inter-Partes examiner?

A. Yes, I did.

Q. Okay. What is a Inter-Partes and protest examiner?

A. That was a group of examiners that was set up to handle allegations of inequitable conduct before the Patent and Trademark Office.

Q. Was it also known as the fraud squad?

A. Yes, it was.

Q. And what period of time did you work as an Inter-Partes -- protest and Inter-Partes examiner?

A. I think sometime between -- from 1980 to about 1983.

Q. And during that time you were an Inter-Partes examiner, did you also act as a staff for the Assistant Commissioner of Patents?

A. Yes.
Q. And what were your duties in that regard?
A. Well, sometimes there were legal problems the Assistant Commissioner would have that he didn't want the Solicitor's Office to handle, and we would advise him on that. At times when there were very hairy things in the Patent and Trademark Office, like regarding genetic engineering, whether we should even grant patents on that, he formulated a committee and put me on the committee, and I worked on that aspect of it.
Q. Did your duties involve the MPEP in any way?
A. Yes. We put in a section of the MPEP that had to do with the inequitable conduct, and we put some guidelines in, and I wrote some of the guidelines in there, along with a group of other people.
Q. And what is the MPEP?
A. It's a group of -- it's a very large book. It sets forth all the procedures of the Patent and Trademark Office and how examiners should handle things and how attorneys should handle things.
Q. Okay. Mr. Goolkasian, you worked for the Patent Office. Is it okay if I just call it PTO at times today? You'll understand what I mean?
A. I'm sorry? Yes. If you call it the PTO, yes.
Q. I understand that you have a slide presentation

prepared for your examination today.
A. Yes.
Q. Okay. Do you have a slide on the functions of the PTO?
A. Yes.
The function of the PTO is really to examine patent applications to determine whether or not they meet the statutory requirement.
Q. Okay. And who participates in the patent examination process?
A. It's an examiner, and the attorneys are agents for the appellant, and it's an ex parte process.
Q. Okay. Does the Patent Office have goals that it strives to meet?
A. I think there are two central goals the Office tries to meet.
Q. Okay. Do you have a slide on that?
And what are those goals?
A. The first goal is to grant valid patents as quickly as possible after filing, and the second goal is consistency in patentability decisions.
Q. What does the Patent Office do to meet its goals of granting patents as quickly as possible?
A. Well, the first thing they do is, they try to get the examiners to examine as rapidly as possible, but you can

only push people so far; otherwise, the quality drops off. So the next thing they do is to try to shift the work off to the practitioners who are dealing with the Patent and Trademark Office, and the rules regarding the duty of disclosure work very well on that basis because they give the examiners a lot of prior art that they wouldn't ordinarily be able to get through their search systems, and you get prior art from other countries who are working on the same patent or counterpart patent applications, and it all filters in to the Office, so you get -- you expand your research facility, the assumption being that if the examiner has the reference, he'll make the correct decision.

Q. Who gives this art, the prior art to the examiners?

A. Generally speaking, the attorneys and the agents who are practicing before the Office. They do this in the form of an information disclosure statement, and they get this prior art sometimes from their own searching, from the inventors, or from foreign patent offices.

Q. Now, the second goal you have up there is "Consistency." What is consistency?

A. Well, this is kind of important, because you want every applicant treated in the same way. You want every decision to be as close to the other decision -- next decision as it can be. You think of it. If you have 2,000 examiners in a Patent and Trademark Office, each examiner is

going to have his own little idea of what obviousness is and what patentability is. You don't want that. You want everybody to have the same idea of what obviousness is and what patentability is.

Q. Okay. Let's talk about consistency a little more. I think you have a slide on that.

Can you tell us how the PTO maintains consistency in its patent examination?

A. All right. It has a section of rules, a set of rules, 37 C.F.R., and they've been codified, and everybody operates by those rules. There are -- you can ask, petition the Commissioner to waive the rules in exceptional circumstances, and that will happen, but only in exceptional circumstances.

Next is, we have a Manual of Patent Examining Procedure, and the manual sets forth all the procedures for -- essentially for practicing under the rules, and everybody is supposed to know what's in the manual.

Then you have examiner training. Examiners are trained, both legally, through a Patent Academy that they have, or they are trained by hiring technical people to come in and sometimes teach them the technology. For example, when biochemistry and genetic engineering first came in, we had numerous people came in to teach the examiners genetic engineering, basic genetic engineering.

Q. Mr. Goolkasian, did you ever teach at the Patent Academy?

A. Yes. I taught several times. I taught the basic course a few times. I taught the section on 35 U.S.C. 112, enablement. And I taught -- I was once chief instructor of the Academy.

Q. Okay. Please continue.

A. Next you have supervisory examiners, and these are picked from amongst the better examiners, and they work closely with the directors and with the examiners, and they supervise the work done. They train the young people, teach them about patentability, teach them how to examine, and they make sure that the older people who have full signatory authority and are primary examiners are doing their work properly.

Q. Mr. Goolkasian, were you ever a supervisory examiner?

A. Yes, I was a supervisory examiner on two separate occasions.

Q. And how are supervisory examiners kept updated?

A. I'm sorry, I didn't hear that.

Q. How are supervisory examiners kept updated?

A. The supervisory examiners, indeed the whole examining corps gets the USPQs, they are sent down all the time, and they read them and they discuss them so they know what the Court decisions are.

Also, the supervisory examiners talk to the directors, and the directors are looking always at what comes down from the Board of Appeals. And so they're having legal meetings as to what the position of the Office is on various issues, and they send -- they transmit this down to the examiners at their meetings.

Q. Okay. You mentioned the USPQ. What is the USPQ?

A. It's a compilation of cases, like the U.S. Code or -- not the U.S. Code, but it's like any of the Federal Digest Reporters or something like that.

Q. All right. Next up, you have "Quality Review." What do you mean by quality review?

A. The quality review for -- for patent applications that have been allowed, they do a random sampling of the patent applications, and first our group checks to see whether everything has been done properly according to the rules and according to the manual, according to the procedures. And then on a few cases, even lesser sampling, they look at the actual decisions being made to see whether or not those decisions are appropriate. And then sometimes they'll even research the case to see whether the examiner found appropriate prior art.

Q. Okay. Next up there is "Board of Appeals." How does that help maintain consistency?

A. The Board of Appeals tries to write each of its

opinions to teach the examining corps what the law is as they see it from what the Federal Circuit says, because the Federal Circuit determines what the Board of Appeals can do. And even if you disagree with the Federal Circuit, you have to follow it. So that happens sometimes.

And they try to write the decisions to train the examiners, so they try -- have consistency in decisions.

Q. Did you ever serve on the Board of Appeals?

A. Yes, I spent 10 years on the Board of Appeals.

Q. About how many cases did you preside over?

A. Well, I think in the 10 years, I can say I -- with a certainty I wrote at least a thousand, maybe 1,200 opinions, and I probably sat on about 3,000 cases.

Q. Okay. You mentioned the MPEP. Do you have a slide regarding the MPEP and consistency?

A. Yes.

Here, this is a section of the MPEP, it's section 700, and it refers to patentability or examination, how examiners are expected to examine.

Section 706 specifically says: "The standards of patentability applied in the examination of claims must be the same throughout the Office."

That means chemical cases are treated the same as mechanical cases, the same as electrical cases; that is, the law applies, the same law applies to all of them.

Q. Okay. Is there anything else in the MPEP that relates to the PTO examination?

A. Yes. There's a section that applies to the Board. The Board is very interested in whether or not it -- it knows about other decisions that the Board makes.

Q. And what section do you have?

MR. BURWELL: Your Honor, I'm going to object. There was no discussion in Mr. Goolkasian's expert report about appeal briefs and requirements of appeal briefs, and I would object that we did not receive fair notice that this was going to be the subject of his testimony.

THE COURT: Is this something that -- I mean, this is technical in nature. It's the manner in which we go through the PTO. Is it something that -- I find that this is something that you could have had notice of or be aware of as a result of the fact you knew he was coming in to testify on inequitable conduct.

No, I'll overrule the objection.

Go ahead.

MR. CLEMENT: Thank you, Your Honor.

Q. So is there some other section, Mr. Goolkasian, that relates -- of the MPEP that relates to PTO examination and consistency?

A. Yes. This is the section regarding preparation of an appeal brief, and it says that the Board wants to know

related appeals and interferences, and they want a statement identifying by number and filing date all other appeals or interferences known to the appellant, et cetera, which will directly affect or be directly affected by, and here is the one that I think is important: "...or have a bearing on the Board's decision in the pending appeal." If the Board decides A is unpatentable in one case, and another case comes up having to do with B, you have almost the same fact situation, then the Board wants to decide that B is also unpatentable.

Q. Okay. And what section of the MPEP is this?

A. Pardon?

Q. For the record, what section of the MPEP is this?

A. That's section 1206.

Q. (c)(2)?

A. Yes.

Q. And this was -- this section was in effect in July of 1996?

A. Yes.

Q. Is it still in effect?

A. Yes, it still is in effect.

Q. Okay. What happens if there are inconsistent decisions of the Board on similar facts?

A. Well, two things -- three things could happen. Number one, if we allow a case one time and then we reverse the --

we reverse the examiner one time and that means the case gets allowed, or we affirm the examiner a second time on a similar fact situation, quite often, the corporations will tell us that, hey, look, you guys are making the wrong decision. That could happen. The directors very often will tell us that, look, you guys are not being straight with us, you come up with different decisions in similar cases, and the Solicitor's Office could also tell us that. They could be brought in.

What happens in that situation is, we formed a five-man panel, and that five-man panel would decide the case, and once that case was decided, then that would have to be followed, their decision would have to be followed by the entire Board.

Q. And did you ever serve on one of those five-man panels?

A. Yes, fairly often.

Q. What are the -- what are the -- what standards govern the -- or what governs the standards applied by the Patent Office in making its patentability determinations?

A. The Patent Office uses the Graham v. John Deere standards, and they've set forth guidelines as to patentability.

Q. And have there been any recent changes to the standards applied by the Patent Office?

A. Yes.

MR. BURWELL: Your Honor, I object. This testimony is going into the current state of the law, apparently, and does not appear relevant to the standards that were applied during the prosecution of the patent-in-suit. We understood he would be testifying about the prosecution of the patent, and the current state of the law as to obviousness would not be relevant.

MR. CLEMENT: Well, I think it's going to show how the Patent Office applies the law to --

THE COURT: But he's saying it's not timely. This patent was prosecuted when; '95?

MR. CLEMENT: '95-'96.

THE COURT: And now you're talking about law as of today. What's the bearing on that on '95-'96?

I think I'm going to limit you as to what was the law at the time the patent was being prosecuted.

MR. CLEMENT: Okay.

Q. Okay. I want to go back to a statement you made earlier, Mr. Goolkasian, about how the applicants provide information to the Patent Office. Do you recall that?

A. Yes.

Q. Okay. Does the Patent Office have rules on the duty of disclosure?

A. Yes. They're set up in Rule 56, it sets up a duty of

disclosure rule.

Q. Okay. Do you have a slide on that, slide nine?

Okay. What is the duty of disclosure, duty of candor?

A. It's a duty to provide to the examiner information that would be important to the examiner in considering whether or not to allow a case or to grant a patent. That's what the rule is. It's Rule 56, and it supplements information unavailable to the examiner through PTO searches. That's one of the big -- good things about it. Ordinarily, in foreign countries, they would have an opposition proceeding, and that's very lengthy, and this hopefully supplements all the information.

Q. To whom does the duty of candor apply?

A. It applies to the applicant, the attorney, and anyone substantively involved in the prosecution of the application.

Q. Okay. And who did it apply to with regard to the '590 patent?

A. It would have applied to the inventor -- inventors in the '590 patent; it would have applied to the attorney, Mr. Jones, and to Mr. Titus, an agent.

Q. And did you review the patent prosecution history for the '590 patent?

A. Yes, I did.

Q. What is the patent prosecution history?
A. A patent prosecution history is a collection of all the writings having to do with that patent application. It includes the specification, the initial claims, and the rejections, the office actions by the examiner, and responses by the applicant, and any IDS's or other information.
Q. In your opinion, what type of things should be disclosed to the examiner to fulfill the duty of candor?
A. To be disclosed, it should disclose the closest prior art, information that would be generally speaking important information from foreign patent publications, and information regarding adverse decisions in similar cases.
Q. In reviewing the '590 patent prosecution and the materials related to this case, did you see anything that you believed should have been disclosed to the Patent Office but was not?
A. Yes. I saw two things. One was the Board opinion in an earlier case, or a copending case, actually, but the opinion was earlier, and the other was a failure to disclose a tandamine reference which had been cited in a foreign prosecution.
Q. Let's talk first about the Board opinion.
Who was the attorney that you believe breached the duty of candor regarding the Board opinion?

A. That was Attorney Jones.
Q. Okay. And how do you know that Attorney Jones owed a duty of candor with regard to the '590 patent?
A. Well, he filed the application. You can see his name here. This is the application transmittal form, letter, and he filed it, and he put his telephone number down on it. When the attorney puts his telephone number down, that means they should call him in case they want to allow it on the first Office action, something like that.
Q. And this is from the patent prosecution history, DTX-2 at STPAT page seven?
A. Yes.
Q. Okay. Do you know of any other documents that show Attorney Jones was involved in the '590 patent?
A. Yes. This is -- there is another -- another document here. This is the Declaration and Power of Attorney, and at the very bottom, in the right-hand side, it says direct telephone calls to Joseph Jones and gives a telephone number again.
Q. And this is from the prosecution history, DTX-2 at STPAT page 18?
A. Yes.
Q. And what about any other documents that show that Attorney Jones was involved in the '590 patent?
A. The next document you see would be a Response to an

Office Action, and this tells me that his actions weren't just merely ministerial, they were actually substantive, because here he is actually writing a response to the office action and telling why he thinks it's patentable.

Q. And this again came from the file history, DTX-2 at pages 33 to 37?

A. Yes.

Q. Okay. What was it that Attorney Jones failed to disclose to the Patent Office?

A. He failed to disclose an earlier Board opinion in a case having to do with the use of atomoxetine for its norepinephrine reuptake inhibition properties as a treatment for enuresis.

Q. Is this an MPEP section that talks about disclosing Board opinions?

A. Yes. This is the section on inequitable conduct, and it advises that the information relating to or from copending United States Patent Applications should be brought to the attention of the examiner or other Office official involved with the examination of a particular application.

Q. Okay. And this came from DTX-202?

A. Yes.

Q. And that's an MPEP section that was in force in January of 1995?

A. Yes, it was.
Q. Do you know why this is required?
A. Well, why this is required is because quite often, applicants will have a group of applications in the Office on similar subject matter and will get rejections by one examiner and allowances or no rejections by another. And they want to have consistency, so they want the examiner who's not rejecting to know that it's been rejected by someone else.
Q. Okay. And what was the prosecution history? What patent was it that the Board opinion appeared in that Mr. Jones did not disclose to the Patent Office?
A. That was a patent we could call the '985 patent.
Q. Is that up on the Board now?
A. Yes.
Q. And is that DTX-6?
A. Yes. It's a patent to Foreman, and it's number 5,441,985, and it's directed to "a method of treating urinary incontinence comprising administering to a human suffering from urinary incontinence an effective amount of tomoxetine or a pharmaceutically acceptable salt thereof."
Q. And did you also review the prosecution history for this patent?
A. Yes, I did.
Q. And is that at PTX-293?

A. Yes, it is.
Q. Okay, and was the claim that was pending at the time -- is the claim that was pending at the time of the Board opinion up on the screen?
A. Yes. That's claim 6.
Q. Okay. And did that differ from the claim that was finally issued?
A. Not significantly.
Q. Okay. Why would a patent directed to urinary incontinence be material to the '590 patent?
A. Because the mechanism by which it's treated is the same mechanism, namely, norepinephrine reuptake inhibition, and that's very important, because ordinarily you might say, what does urinary incontinence have to do with ADHD? But remember, it's the mechanism of operation, and that's what's going to be important to the Office.
Q. Okay. We also have the '590 patent up there; correct?
A. Yes.
Q. Okay. Is there any comparison between those claims?
A. Yes. The '590 patent says "a method of treating attention deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of tomoxetine." So aside from the fact that the problem being treated is different in both cases, the actual drug being administered and the administration

technique is the same.
Q. Okay. Are there any other reasons why you believe this urinary incontinence material would be relevant here?
A. Oh, most definitely. In fact, I think Mr. Jones believed it was material.
Q. And how do you know that?
MR. BURWELL: Objection, Your Honor.
THE COURT: I'll sustain the objection as to what Mr. Jones believed.
MR. CLEMENT: Okay.
MR. BURWELL: And I'd also object to any testimony concerning this Springer reference. This was not identified in his expert report either as a basis for any opinion that he was going to offer at trial, and we were never afforded the opportunity to cross-examine him at his deposition on this issue.
MR. CLEMENT: It's in the file wrapper. It's in the patent '590 file wrapper, and I believe that Mr. Goolkasian discussed the IDS in the file wrapper.
THE COURT: Am I correct in assuming that when he listed that which he relied upon for his expert opinion, he listed the PTO file wrappers?
MR. CLEMENT: Yes.
THE COURT: I'll allow it.
Q. Okay. Did Mr. Jones cite a urinary incontinence

patent to the Patent Office?
A. Yes, he did.
Q. And how do you know that?
A. Because when I looked at this, I saw Springer, and it said urology, and I said, well, what does that have to do with this subject matter? Until I looked at what it said. It was "Facilitatory and Inhibitory Effects of Selective Norepinephrine Reuptake Inhibitors on Hypogastric Nerve-Evoked Urethral Contractions in the Cat." And this is -- so this is being sent in because the attorney is sending in material information to the Patent and Trademark Office. So they put the urology thing in there. The only assumption I could make is that at that time, it would have been material. Otherwise, it's foolish to put it in.
Q. This information disclosure statement was found at DTX-2, STPAT 29 to 30?
A. Yes.
Q. Can you explain to the Court what an information disclosure statement is?
A. Yes. The information disclosure statement is a way that applicants and their attorneys can comply with the duty of disclosure. The information disclosure statement lists references that they believe could be material, that a reasonable examiner would want to know in examining the application. And these are the references listed. For

example, the Springer reference is listed down at the bottom there, all of those things that were talked about by Mr. Lipsey this morning, physicians' Desk References, I think, all of those were before the examiner, too, in this IDS. So the examiner knew about those things.

Q. Is the information in an IDS supposed to be correct?

A. Pardon?

Q. Must the information in an IDS be correct?

A. Yes.

Q. Are patent attorneys supposed to cite nonmaterial art to the Patent Examiner?

A. Hopefully not.

Q. And why not?

A. Because it just increases the amount of work the Office has to do.

Q. Was there something else in the '590 patent prosecution you're relying on to say the Board opinion in the urinary incontinence patent was material to the '590 patent?

A. Yes.

Q. And what is that?

A. The examiner cited the Ryan reference. And when you read the Ryan reference, he shows that the norepinephrine reuptake inhibition --

MR. BURWELL: Objection, Your Honor. He's now

giving technical testimony, and he's not qualified as a technical expert to provide such testimony.

MR. CLEMENT: I think he's explaining what the examiner did.

MR. BURWELL: He's talking about what the Ryan reference disclosed.

THE COURT: Could I have the beginning of what he was saying?

(Record read)

THE COURT: Well, it sounds like he was talking about what is in the Ryan reference, doesn't it?

MR. BURWELL: Right, and he does not have the technical background to understand that.

THE COURT: How about it?

MR. CLEMENT: I can move on.

THE COURT: Good.

BY MR. CLEMENT:

Q. Okay. Mr. Goolkasian, did you review the '985 patent file history?

A. Yes, I did.

Q. Okay. Is the '985 prosecution history relevant to the '590 examiner's reasons for rejecting the application?

A. In my opinion, it is.

Q. And why is that?

A. Because it sets forth the rationale for the Board of

Appeals in this type of substitution of one chemical for another.

Q. And was that rationale found in an Office action?

A. Yes, it is.

Q. And was that the Office action PTX-293, page 65?

A. This now is the examiner's rationale, but it's very similar to the Board's. The examiner says that the applicant had made some remarks regarding the combination of references by saying they weren't structurally similar chemicals, and the examiner says the "Remarks regarding the structure of tricyclic drugs are not well taken since the rejection is not based upon the similarity of the structures of the drugs, but rather the mechanism of action and the information taught regarding the norepinephrine uptake inhibition."

Q. Okay. Did Attorney Jones ever appeal that decision?

A. Yes, he did.

Q. Okay. What we have up on the screen, is that the letter transmitting a brief on appeal?

A. Yes.

Q. And that's at PTX-293 at pages 74 to 79?

A. That's correct.

Q. Okay. What is an appeal?

A. An appeal is a case wherein the examiner has decided that a subject matter before the examiner is not patentable,

at least some subject matter, and the examiner has finally rejected the claims, and once claims have been twice rejected, the examiner can -- the applicant can appeal the rejection, and the applicant decides to go to the Board to see if the Board will overrule the examiner and say that it is patentable, whereas the examiner has said that it was unpatentable.

Q. Okay. And what was the claim that Mr. Jones appealed? Is that up here on the Board?

A. Yes. That's the same claim 6 we saw before.

Q. Okay.

A. "A method of treating incontinence, et cetera, comprising administering to a human suffering from incontinence, et cetera, an effective amount of tomoxetine or a pharmaceutically acceptable salt thereof."

Q. Okay. And we already discussed how that compared to claim 1, so we'll move on from that.

Did this appeal proceed to a Board opinion?

A. Yes, it did.

Q. Okay. Do you have a slide on that Board opinion?

A. Yes.

Q. And what did the Board say?

A. The Board was going -- I first started talking about the argument that was made, the rationale that was made by the appellant in that case. They say: "We do not consider

the rationale to be well taken. One having ordinary skill in the art would have been taught by the applied references that tomoxetine was known in the prior art to inhibit norepinephrine uptake (again see, for example -- " -- they used the Zerbe reference in that -- " -- and that the inhibition of norepinephrine uptake was known in the prior art to control incontinence," et cetera. And they cited Cohen for that.

"Further, norepinephrine uptake inhibition is only one factor which would have been considered in selecting a compound for use in treating the disorders in question. Other factors such as side effects would have been considered, and Zerbe's teaching that tomoxetine produces relatively mild side effects would have militated for use of this compound for treating these disorders."

Q. Okay.

A. In other words, the Board is saying because they have the same mechanism of action, it's obvious to substitute one chemical that works by the same way for another chemical that works by the same way. And then they said also, look, if you have lesser side effects, that's good, that's one reason to use it.

Q. Okay. And this is the Board opinion at DTX-210, and the pages that you're reading from are from pages 87 to 89 --

A. Yes.

Q. -- for PTX-293?

And why are these statements material to the '590 patent in your opinion?

A. Well, because the examiner had made a very similar rejection in his case dealing with ADHD, and had the examiner known that the Board would have affirmed that rejection, the examiner would never have allowed those claims.

Q. Okay. Have you prepared a slide with the side-by-side comparison?

A. Yes. The Board's opinion in the '985 patent application is on the left-hand side, and the examiner's opinion is on the right-hand side in the '590. And you can see both sides, "tomoxetine was known in the prior art to inhibit norepinephrine uptake. And "the inhibition of norepinephrine uptake -- " -- and the examiner just simply called that monoamine uptake -- " -- was known in the prior art to" in one case control incontinence, in the other case to treat ADHD.

And then he said: "Other factors such as side effects would have been considered, and Zerbe's teachings that tomoxetine produces relatively mild side effects would have militated for use of this compound...."

Ryan said "tomoxetine was known to have

'potentially fewer side effects.'"

Q. Do you have another slide to show how the rationale from the Board opinion in '590 were analogous?

A. Yes, I do. This takes the Board opinion, just substitutes -- it's going to substitute the examiner's reasoning and references.

MR. BURWELL: Your Honor, I object to this slide and the one before it and the whole substitution that just happened. After this substitution, the language in the upper portion of this slide does not accurately reflect the rejection that was made by the examiner during the '590 patent prosecution.

MR. CLEMENT: I think it accurately reflects that. It's my understanding it completely accurately reflects it.

MR. BURWELL: The slide he just talked about said that the examiner's rejection of the '590 patent application talked about the inhibition of monoamine uptake, and he's now changed the words "monoamine uptake" to "norepinephrine uptake was known in the prior art."

That's completely inaccurate.

MR. CLEMENT: Norepinephrine is a monoamine. I don't see where it's changed much. I think Mr. Goolkasian is just showing how the decisions were analogous.

THE COURT: I'm going to allow it.

BY MR. CLEMENT:

Q. So, Mr. Goolkasian, how did this slide show that one rationale from the Board opinion was analogous to the '590?

A. Yes, it does. It also shows what the law was back at that time, because -- what the Board would have factored according to the law.

Q. Is it your opinion, Mr. Goolkasian, that the Board decision was material to the '590 patent application?

A. In my opinion, it most definitely was material to the '590 application.

Q. Now, you were present at Dr. Berridge's testimony yesterday?

A. Yes, I was.

Q. And you heard his testimony on urinary incontinence?

A. Yes.

Q. Does that change your opinion as to the relevance of the Board opinion?

A. No, not at all. I think it's very unfair to ask technical witnesses information about patent law, and he's a technical expert. And in the Patent Office, we get questions of analogous side, one analogous side all the time. And the Patent Office is considering here the mechanism of the way the drug works, and that's what's important, not the fact that the disease or two somewhat dissimilar diseases, you might say. But that's essentially

it. The Office is concerned with the way the drug works.

Q. Okay. I'm sorry. I guess I didn't identify for the record this Board opinion one that we were looking at: PTX-293 at 87 and 89.

All right.

MR. BURWELL: I'm sorry, I have to object. This statement that is now on this slide is not present in --

THE COURT: This is the transfer of --

MR. BURWELL: This is after his substitution, and this statement on the slide does not appear in any trial exhibit.

THE COURT: Isn't that so?

MR. CLEMENT: That's true, yes.

Why don't we flip back to before we changed it? That slide accurately reflects PTX-293?

MR. BURWELL: We're okay with that slide.

MR. CLEMENT: Thank you.

BY MR. CLEMENT:

Q. All right. Now, Mr. Goolkasian, did you find any evidence from which one might be able to infer that Mr. Jones had an intent to conceal the Board opinion from the examiner?

MR. BURWELL: Again, objection as to testimony regarding intent.

THE COURT: I'll sustain that.

MR. CLEMENT: Okay. I don't think I'm asking about Mr. Jones's state of mind, just circumstantial evidence from which intent could be inferred.

THE COURT: I don't know how I divide that up.

I'll sustain that objection.

Q. Mr. Goolkasian, what happened after the Board's opinion?

A. After the Board's opinion, he refiled the case. Actually, he refiled the case before the Board's opinion but forgot to tell the Board, and so the Board went through its process of deciding the case. And then he saw the opinion came out, and he tried to get it withdrawn, he tried to get it -- the Board to take away its opinion, and he says, "The undersigned realizes -- " -- he wrote a letter to request the Board to withdraw the appeal, and in that request, he said: "The undersigned realizes the significance of his oversight and assures the Board that the error will not be repeated..."

Q. This is from PTX-293 at pages 105 to 106?

A. Yes.

Q. Have you ever come across one of these withdrawal requests during your 25 years at the Patent Office?

A. Well, such withdrawal requests are very rare. They're not usually made because they're -- when you refiled the case, they're going to be in the file anyway and the

examiner's going to know what the Board's opinion was. So they're not usually done.

THE COURT: So what's the reason for filing the withdrawal?

THE WITNESS: I -- honestly, Your Honor, I can't figure why he asked for that.

THE COURT: All right. Go ahead.

Q. What did the Patent Office do with Mr. Jones's request to withdraw?

A. It denied it.

Q. And we have that --

A. This is a letter from Fred McKelvey, the Chief Judge.

Q. And this is at PTX-293 at pages 114 and 115?

A. Yes.

Q. Mr. Goolkasian, is it your opinion that Attorney Jones breached his duty of candor with regard to failing to disclose the Board opinion?

A. Well, if you look at it, he -- he knew of the Board opinion, he knew of its significance, and he didn't submit it.

MR. BURWELL: I'll object to his testimony concerning knowledge of the significance of the Board's opinion.

And while the slide is up, I'll object to any testimony concerning evidence of intent.

THE COURT: Yes, I don't know how he can testify as to what he knew.

Why don't you go back to that question and answer, the question that's asked, the original question that you asked?

MR. CLEMENT: Okay. Could you repeat the question for me? Thank you.

(Record read)

A. Yes.

Q. Did Mr. Jones know about the Board opinion?

A. Yes.

Q. Did he prosecute the '590 application?

A. Yes, he did.

Q. And what was the -- did you find a comparison between the two?

A. Yes, the fact situation -- from the Board's viewpoint, this -- from the Board's viewpoint, the legal situation was exactly the same.

Q. All right. Let's turn back to -- let's go to slide 27 regarding the instances of a breach of duty of candor that you found in the second one, slide 27.

A. Okay.

Q. Okay. What was the second instance of breach of duty of candor that you found?

A. This is a failure to disclose the tandamine reference.

Q. And where did the tandamine reference appear?
A. The tandamine reference appeared during prosecution of a counterpart application in the European Patent Office, and it was in a search report that was given to Lilly regarding that application.
Q. Okay. What is a foreign counterpart?
A. It's an application filed in a foreign country that has, generally speaking, usually the same specification and claims as in the U.S. case.
Q. Okay. Are there any PTO guidelines regarding foreign counterparts?
A. Yes. The PTO wants to see references that are cited in that foreign case.
Q. And how do you know that?
A. This is a section of the MPEP, it's 2001.06, and it says: "Applicants and other individuals, as set forth in 37 CFR 1.56, have a duty to bring to the attention of the office any material prior art or other information cited or brought to their attention in any related foreign application." And it says: "The inference that such prior art or other information is material is especially strong where it has been used in rejecting similar claims."
Q. In the foreign application?
A. Yes.
Q. Which section of the MPEP did this come from?

A. It came from -- this, again, the duty of disclosure section, it's 2001.06(a).

Q. Okay. And that's DTX-202?

A. Yes.

Q. Okay. Next slide, did you prepare a timeline for us so we can see how the events occurred?

A. Yes.

The application was filed in January 11th, 1995, this is for the '590 patent, and the European application was filed a year later, on January 9th, 1996.

On October 8, 1996, a different individual, Mr. Titus, a patent agent, he submitted a brief in the '590 -- appealing the '590 final rejection.

Q. Okay. Weren't we talking about Mr. Jones before? Where did this Mr. Titus come from?

A. Yes. Apparently Mr. Jones was no longer on that case, and the case was parsed out to Mr. Titus.

Q. And how do you know that Mr. Titus became involved in the prosecution of the '590 patent?

A. Because his name appears on the brief.

Q. Okay. And is this the brief at DTX-2 STPAT 44-51?

A. Yes. And if we look, we see this docket number X-9726. That's on almost all the papers in that file, and it's also on papers in the European application file.

Q. Is that a Patent Office docket number, or is that

internal?

A. That's a training docket number.

Q. And this does show that Mr. Titus was responsible for this brief?

A. Yes.

Q. Okay. And did you review the appeal brief?

A. Yes, I did.

Q. Did the brief argue for separate patentability of the dependent claims?

A. No, it did not. Here we have the examiner rejected the claims under 35 U.S.C. 103, he treated claims 1 through 16 as a unit, and the Board -- the appellant, with the Board, he grouped the claims as a unit, which means that as far as the Board and the examiner are concerned, claims 2 through 16 do not offer anything which is patent -- makes claim 1 patentable.

Q. So the quote at DTX-2, STPAT 26, that came from the examiner?

A. Yes.

Q. And the one at DTX two, STPAT 45, that came from Mr. Titus?

A. Yes.

Q. What does that mean, that the claims stand or fall together?

A. That means that the applicant is willing to accept

that there is nothing in the dependent claims 2 through 16 which makes claim 1 patentable.

Q. Going back to the timeline, what's the next time point?

A. December 23rd, 1996, the examiner allowed the application for the '590 patent. And then on January the 17th, the European Patent Office issued a search report on the counterpart application.

Q. Okay. Let's go back to the December 23rd, 1996 date. Did Mr. Titus's duty to disclose end then?

A. No. The duty to disclose continues until the patent is granted.

Q. And how do you know that?

A. Pardon?

Q. And how do you know that?

A. Because it's in the rule.

Q. And your timeline also shows that the European search report issued?

A. January 17th, 1997.

Q. Okay. Did you prepare a slide regarding the European search report?

A. Yes.

Q. Mr. Goolkasian, what is a European search report?

A. In foreign countries, even in the United States now, but in the foreign countries, at least back then, and even

then, I guess, they do a search report first. That gives the patent owner the opportunity to see what prior art they have found in the Office so the owner can decide whether or not to continue prosecution of that application. But there is no office action on it and there's no application of the prior art or the claims. It's just a statement of what they thought was the closest prior art.

Q. Okay. And this is found, this European search report is found at DTX-257 at STPAT 406 to 407?

A. Yes.

Q. Okay. And are there E references listed on that European search report?

A. Yes.

Q. What is an E reference?

A. An E reference is stated right at the bottom where it says "Category of Cited Documents." It's an earlier patent document, but it's published on or after the filing date, so it's not really a reference.

Q. Okay. And what about, is there -- were there Y references on that search report?

A. Yes. A Y reference is a reference that's considered by the examiner to be particularly relevant if combined with another document of the same category.

Q. And what is the Y reference that you have highlighted there?

A. The Y reference is a reference having to do with tandamine, a new norepinephrine reuptake inhibitor.
Q. Okay. Going back to the timeline, what is the next point?
A. The next point is, Titus -- we know that Titus received the search report on February the 11th, 1997.
Q. Well, I think we have a time point January 28.
A. Oh. I'm sorry. I just didn't see that.
January 28, Lilly in the U.K. sent the search report to Titus.
Q. Okay, and then Mr. Titus received it when?
A. Yes, he received it on February the 11th, 1997.
Q. And how do you know this?
A. Because he initialed it.
MR. CLEMENT: Okay. Can we have that?
Q. Is this the document from which you know it?
A. Yes. He initialed it. It shows his initials. It shows he got a copy of the search report, it was enclosed with this cover letter, and a copy of the citations is also enclosed.
Q. Okay. This is DTX-212?
A. Yes.
Q. And how do you know this is relating to the European search report?
A. Because it's got this docket number. Remember this

X-9726? They just put an "EP" after it, which means European.

Q. And does this say that this also enclosed a copy of the citations?

A. Yes.

Q. And did this all occur before the '590 patent issued?

A. Yes.

Q. Okay. Were there any other documents showing that -- were there any other documents showing that '590 and the European application were counterparts of each other?

A. Yes, there were.

If you look at the '590 patent, it has an application serial number 371,341, filed January 11, 1995, and this is the European published application. It claims priority of the same serial number 371,341, which is down at, marked 30, so it's the same priority application.

Q. Okay. And you're looking at DTX-224 at STPAT 944333?

A. Yes, and someone has put in hand, again, that X-9726 number up in the upper right-hand corner.

Q. Can we just go back quickly to slide 34? I think I didn't say something -- or I didn't say something correctly for the record.

Mr. Goolkasian, this European search report was found at DTX-277 at STPAT 945406 to 407?

A. Yes.

Q. Thank you. Sorry.

Mr. Goolkasian, is it your opinion that the tandamine reference is material?

A. Well, it's a Y reference, and Y references are usually considered material.

Q. And you mentioned earlier that Mr. Titus was involved in the '590 prosecution; correct?

A. Yes.

Q. So is it your opinion he owed a duty of candor to the Patent Office with regard to the '590 patent?

A. Yes.

Q. And did the prior slides we saw show he had knowledge of the European search report and the tandamine reference?

A. Yes.

Q. Did Mr. Titus ever submit the European search report or the tandamine reference to the Patent Office?

A. No, he did not.

Q. Could he have?

A. Yes, he could have. There's a procedure where one simply files a petition and pays a fee, and the Office will look at it.

Q. Did you find evidence that he filed that procedure in other cases?

A. Yes.

Q. Okay. In what other cases?

A. There were two other cases. One was the '070 patent, and the other was the '222 patent.

There's a third one, too. There's a Canadian counterpart application.

Q. Okay. Let's take a look at the '070 first. Did you review the '070?

A. Yes, I did.

Q. And the prosecution?

A. Yes.

Q. And the '070 patent is up there on the screen now?

A. Yes, it is.

Q. And that's DTX-7?

A. Correct.

Q. And what is this patent about?

A. This is a treatment of oppositional defiant disorder using tomoxetine. Atomoxetine, it has here.

Q. And does it have the same inventor as the '590?

A. Yes, it does.

Q. And does it list the same attorney?

A. Yes, it does.

Q. Okay. What happened in that '070 prosecution history?

A. In that prosecution history, a European search report came in, and it was submitted to the examiner after a notice of allowability.

Q. And the '070 prosecution history, that's PTX-301?

A. Yes.
Q. Okay. And this notice of allowance is found at PTX-301 at page 69 and 70?
A. Yes.
Q. Was this a submission of a European search report after the application was allowed?
A. Yes, it was.
Q. And how long after the search report was issued by the European Patent Office did Mr. Titus submit it to the U. S. Patent Office?
A. Well, he submitted it within the three-month window. You have a three-month window of opportunity to send it from the time the search report was issued by the foreign patent office till the time you send it in to the Office.
Q. And how do you know that?
A. Well, because as a rule, it says so. It's 37 C.F.R. 1.97(d) and (e), and it's (e) that says about the three months, I believe.
Q. And this rule specifically applies to counterpart foreign applications; correct?
A. Yes.
Q. And this rule was in effect --
A. Well, it applies to any foreign application that you have.
Q. And this was in effect in September of 1995?

A. Yes.
Q. Okay. The other patent you mentioned was the '222 patent?
A. Yes.
Q. And what is -- the '222 patent, that's DTX-8?
A. Yes. This is another invention by Dr. Heiligenstein that goes to the treatment of conduct disorder using drugs, one of which could be tomoxetine, and for the norepinephrine inhibition uptake property, and -- it, too, had a foreign counterpart.
Q. Okay. And did you review the '222 prosecution history?
A. Yes.
Q. Okay. And what happened there?
A. On June 28, 1999, there was a notice of allowability. On July 14th, 1999, Mr. Titus submitted the search report from the European counterpart applications of the PTO.
Q. Okay. And the notice of allowability, that's at PTX-300 at page 80?
A. Yes.
Q. And the information disclosure statement where Mr. Titus submitted the search report from the counterpart application to the Patent Office is at PTX-300 at page 82?
A. Yes.
Q. Okay. What happened as a result of how Mr. Titus

submitted the European search report during the prosecution of this '222 patent application?

A. Well, in this one, he didn't follow that petition procedure and so they didn't accept the IDS form, so what he did is, he filed a continued prosecution application. That's what that is, is, you simply pay a fee and then you're entitled to continue the prosecution. The prosecution is reopened, and you pay the fee, you continue the prosecution. And then he submitted an IDS that contained the references that were cited in the European search report.

Q. Okay. And the PTO rejection of the IDS, that was at PTX-300 at pages 90 to 91?

A. Yes.

Q. And then Mr. Titus's submission of the continued prosecution application was at PTX-300 at page 92?

A. Yes.

THE COURT: How much longer are we going to be, counsel?

MR. CLEMENT: Probably another 10, 15 minutes.

THE COURT: Is this a good time to take a short morning break?

MR. CLEMENT: We can certainly do that.

THE COURT: Okay. Why don't we take about 15 minutes?

You can step down, sir.

(Recess taken)

THE COURT: Be seated.

(The witness resumed the stand.)

THE COURT: Okay?

MR. CLEMENT: Ready to continue. Thank you, Your Honor.

BY MR. CLEMENT:

Q. Mr. Goolkasian, when we left off, I think we talked about Mr. Titus requesting a continued prosecution application to resubmit the IDS?

A. Yes.

Q. Okay. What happened there?

A. So after he -- he didn't get approval of the original one, so he filed a continued prosecution application, I think I testified to that, and then he submitted an information disclosure statement which included in it the references or some of the references that have been cited in the examination report.

Q. The European report?

A. Yes.

Q. And he submitted this information disclosure statement on September 22, 1999?

A. Yes.

Q. And this appears at PTX-300 at pages 97 to 98?

A. Yes.
Q. Let's go back to your timeline.
Okay. So when did Mr. Titus pay the issue fee?
A. I'm sorry, I didn't hear the exact question.
Q. I'm sorry. When does the timeline reflect that Mr. Titus paid the issue fee?
A. Mr. Titus paid the issue fee on March the 17th, 1997.
THE COURT: For the record, that's St. Patrick's Day.
(Laughter)
MR. CLEMENT: Thank you, Your Honor.
Q. And then the patent issued on August 19th, 1997.
A. Yes.
Q. Did the prosecution continue in Europe?
A. Yes, it continued in Europe.
Q. And also in Canada?
A. Yes.
Q. Okay. Was the tandamine reference cited in the Canadian counterpart application?
A. Yes, it was.
Q. Okay. Do you have a slide on that?
A. This is the Canadian counterpart application, and we know that it's claiming the same priority of the 371,341 application filed in the United States.
Q. Okay. And this is -- what Canadian Patent Application

Number is this?
A. It's 2,209,735.
Q. And this is found at PTX-760 at STPAT 944346?
A. Yes.
Q. And this was the counterpart to the '590 patent; correct?
A. Yes.
Q. And how do you know this was the Canadian counterpart?
A. Because it's got this -- all this Canadian information on it, and it refers back to the United States of America application 371,341.
Q. And did you review the file wrapper history for the Canadian patent '735?
A. Yes, I did. I had a redacted version of the file, though.
Q. And do you recall seeing who was involved in the prosecution of the Canadian application?
A. Yes. The Canadian application was prosecuted by a Canadian law firm, but they were dealing with Mr. Titus.
Q. Okay. This is a letter you have up there on the screen?
A. Yes. This is a letter from the Canadian law firm to Mr. Titus, indicating "I enclose herewith, a copy of the request for expedited examination, along with a copy of the Preliminary Amendment as filed."

Q. And this has the same reference number in the Re line, X-9726?

A. Yes.

Q. Okay, and do you know if a European search report was submitted to the Canadian Patent Office?

A. Yes, I do. It was submitted to the Canadian Patent Office.

Q. And how do you know that?

A. Because I've seen it, the document, in the file.

Q. And is where you saw it up on the screen now?

A. Yes, this is the preliminary amendment, and it says that "Applicant encloses herewith a copy of the first page of US Patent No. 5,658,592, a copy of US form PTO 1449, a copy of the International Search Report and of the corresponding European Search Report."

This is the European search report on the right-hand side, and it shows this tandamine reference being submitted to the Canadian Patent Office.

Q. Okay, and the first page of that preliminary amendment, that's found in PTX-760 at STPAT 944375?

A. Yes.

Q. And the European search report is from the same Exhibit at 944381?

A. Yes.

Q. Did you see Mr. Titus stating anything to the Canadian

Patent Office about the lack of materiality of this Y reference?

A. No.

Q. Okay. Now, this document also refers to an International Search Report. Do you see that?

A. Yes.

Q. Okay. Did you review that as well?

A. Yes, I did.

Q. What is a PCT search report?

A. Well, sometimes when -- if someone wants to file a patent application in several different countries, they can file one in a PCT country and designate all the rest, and they get the examination in the country, and what happens is, when they do that, the PCT country that's doing the examination, they do what is called a search report in the same way that European office would do it, and the search report, in this case, the examination country was the United States, and the search report was by Examiner Spear, the same examiner who had examined the '590 patent in the United States, and the search report lists the same references, and they were all Y references, and they were submitted to the Canadian Patent Office.

Q. When you say "same references," what do you mean?

A. This is the references that the examiner had used to reject the claims. This PCT is dated -- has different dates

on it than what the examiner's actual rejection dates are.
Q. And you're talking about the examiner's rejection in the '590 patent?
A. Yes. Yes. But it's the same references, they're all listed as Y, and the examiner just sends -- sends them.
Q. Y: Was that the same category that was given the tandamine reference in the European search report?
A. Yes, it's the same category.
Q. Have you read Mr. Titus's deposition transcript?
A. Yes, I did.
Q. Do you recall him saying that he considered the tandamine reference but did not cite it to the Patent Office?
A. That's correct.
Q. Okay. Is this the testimony you were referring to?
A. Yes. He says that he didn't cite it, and that he made an independent determination about whether the references needed to be cited in the U.S. case.
Q. And this is from a deposition held on September 4th, 2008 at page 61, lines seven to 10, line 17 -- and page 62, lines two to eight?
A. Yes.
Q. Do you also recall him testifying that he did not make a note to the file regarding his independent determination?
A. That's correct. He was specifically asked if he had

recorded this information anywhere, and he said --

THE COURT: You know, counsel, I don't know whether it's appropriate that we're just having him read testimony from somebody who hasn't testified here as a witness.

Is this going to be read into evidence, or what is it?

MR. CLEMENT: We haven't been told whether or not Mr. Titus is going to come to trial.

THE COURT: Well, what rule allows us to just pick up somebody's deposition testimony and read it when they're not a party to the action?

MR. CLEMENT: Okay. We can take it down.

Q. Mr. Goolkasian, do you recall testifying as to whether or not he made a note to the file regarding his independent determination?

THE COURT: Well, that's the same question, it's just that he's not reading the testimony.

Is there an objection to any of this?

MR. CLEMENT: I haven't heard one.

THE COURT: No, neither have I.

MR. BURWELL: Your Honor, I question --

THE COURT: Is this gentleman going to be testifying? Or is his testimony going to be read into the record?

MR. LIPSEY: If I may intercede as in loco parentis --

(Laughter)

MR. LIPSEY: -- we're trying to plan out our case. We have witness availability issues for witnesses who have to be in the Canadian trial in the same action. And Mr. Titus did testify fully in his deposition about these matters. We haven't yet decided --

THE COURT: You have no objection to this?

MR. LIPSEY: The point is, if we don't bring him, we are going to let the deposition come in, and for that reason, I think in fairness to them we ought to allow them to use the deposition.

THE COURT: All right. If that's the situation, okay.

MR. CLEMENT: Thank you.

A. All right. Well, then, I'll read it --

(Laughter)

THE COURT: Spoken like a true lawyer.

(Laughter)

A. It says:

"QUESTION: And do you recall whether or not you made any notes on the -- on the review of the prior art?

"ANSWER: I do not recall.

"QUESTION: When you called upon to produce

documents or look for documents in connection with the production in this litigation?

"ANSWER: Yes, I was.

I misspoke. It says Were You Called Upon.

He says, "Yes, I was."

"QUESTION: I take it you checked to see if you had any notes?

"ANSWER: Yes.

"QUESTION: And you didn't find any?

"ANSWER: I did not."

BY MR. CLEMENT:

Q. Okay. This was from Mr. Titus's deposition at page 63, lines six to 17?

A. Yes.

Q. On September 4th, 2008?

A. Yes.

Q. Okay. Is there an MPEP section that's relevant to this?

A. Yes. This is the "Aids to Compliance With Duty of Disclosure" where the MPEP and the Patent Office tried to tell the bar different things they had to do to make life easier for everybody on inequitable conduct issues, and the very last line says: "If information was specifically considered and discarded as not material, this fact might be recorded in an attorney's file or applicant's file,

including the reason for discarding it. If judgment might have been bad or something might have been overlooked inadvertently, a note made at the time of evaluation might be an invaluable aid in explaining that the mistake was honest and excusable. Though such records are not required, they could be helpful in recalling and explaining actions in the event of a question of 'fraud' or 'inequitable conduct' raised at a later time."

Q. Okay. Did Mr. Titus follow that guideline?

A. No, he did not.

Q. This guideline's found at DTX-202 at pages 2000-8?

A. Yes.

Q. And it's January 1995?

A. Yes.

MR. CLEMENT: I just want to go back quickly to slide 48. It appears I forgot to identify that for the record. This was Gowling's letter to Mr. Titus, Exhibit PTX-770 at STPAT 944379.

Q. Okay. Mr. Goolkasian, when you were here yesterday, did you also hear Dr. Berridge talk about tandamine?

A. Yes.

Q. And did what Dr. Berridge say change your opinion?

A. No, not really. The reference was a Y reference. It seemed to be important enough to give to the Canadian Patent Office. It talks about a new norepinephrine -- by its very

title a new norepinephrine reuptake inhibitor, and so it could very well have been material to a reasonable examiner. Anyway, I think he should have submitted it.

Q. So does it remain your opinion that Mr. Titus breached his duty of candor by failing to submit the tandamine reference?

A. Yes.

MR. CLEMENT: Okay. Your Honor, I just want to move some exhibits into the record.

I have DTX-2, 6, 7, 8, 52, 107, 202, 205, 210, 211, 212, 216, 224, and I have PTX-293, 300, 301, and 760.

THE COURT: Any objection?

I assume these are all of these documents that you've been using.

MR. CLEMENT: Yes.

MR. BURWELL: No objection to these documents.

THE COURT: Into evidence.

(Plaintiff's Trial Exhibits 293, 300, 301 and 760 and Defendants' Trial Exhibits 2, 6, 7, 8, 52, 107, 202, 205, 210, 211, 212, 216 and 224 marked in evidence)

MR. BURWELL: We do reserve objections as to the demonstratives.

THE COURT: Well, he didn't offer them.

MR. CLEMENT: I didn't offer those.

I just have one other housekeeping matter, I

guess.

Can we go back to the PCT search report?

I'm being told that this should have been PTX-760 at 944,377, not 366, I apologize, for the record.

THE COURT: Any objection to the change?

MR. BURWELL: No objection.

THE COURT: Okay.

MR. CLEMENT: I pass the witness.

THE COURT: Cross-examine.

MR. BURWELL: Good morning, Your Honor. Scott Burwell for Plaintiff Eli Lilly and Company.

CROSS-EXAMINATION

BY MR. BURWELL:

Q. Good morning, Mr. Goolkasian.

A. Good morning.

Q. Are you able to hear me all right?

A. I'm sorry?

(Laughter)

Q. I take it the answer is no. I asked you if you were able to hear me okay.

A. Yes, I can hear you okay.

Q. If you are unable to hear me, please let me know, and I'll do my best to speak up.

A. I will.

Q. You've been handed a collection of binders. Among

them are your deposition testimony from this case, your expert report, and some other materials that we may be going into over the course of the cross-examination.

First, I'd like to talk a little bit about your background.

Now, you testified on your direct examination that you have an undergraduate degree in chemical engineering. Is that correct?

A. Yes.

Q. But you don't have any advanced degrees, do you?

A. No, I have no advanced degrees. The only thing that I did have of an advanced nature was that in 1983, after I wrote Ex Parte O'Farrell, I had to really learn to understand biochemistry because I was going to get a lot of genetic engineering cases, so I took a year of biochemistry at the National Institute of Health Graduate School.

Q. Okay. That was a class that you had audited?

A. Yes, I audited it, actually.

Q. You were not actually in the laboratory doing experiments as part of that class, were you?

A. No, I didn't do any of that. I was too old.

Q. Now, you're not a person of ordinary skill in the art as to which the '590 patent-in-suit is directed, are you?

A. No.

Q. And you've never worked for a pharmaceutical company,

have you?
A. That's correct.
Q. And you've got no experience in the medical field?
A. No.
Q. And you're not an expert in neurotransmitters, are you?
A. No, I'm not.
Q. You've got no experience with ADHD, do you?
A. None.
Q. Now, when -- you can't place on these technical references that have been discussed the nuances that a technical expert could, could you?
A. That's correct, I couldn't do that.
Q. And you know nothing about ADHD other than what you've read in the documents that counsel for the Defendants have provided to you; is that correct?
A. I know nothing about ADHD other than what I've read in the documents.

One of the previous questions you asked, I couldn't put the nuance as would a technical person, but I could as would a Patent Examiner, because that's what I did for years.

Q. Now, in the course of your work on this matter, you did not independently look for any other art beyond that what was provided to you by Defendants' counsel, did you?

A. That is correct.
Q. And you have not reviewed in the course of your work on this matter the opinions that Lilly's expert, Dr. Pliszka, has rendered in this case, have you?
A. That is correct.
MR. BURWELL: Could we have DTX-2 up on the screen, please?
Q. And that should be tab one of your binder, volume one.
A. Okay. I see that.
Q. And if I can direct your attention to the page with the Bates number STPAT 23.
A. I am having trouble finding -- okay.
Q. It would be at tab one, the first document in your binder.
A. I hear that.
Q. And there are numbers in the lower right-hand corner of each page.
A. What is the Bates number?
THE COURT: Twenty-three. Have it?
THE WITNESS: No. Sorry.
THE COURT: Counsel, why don't you assist him?
THE WITNESS: Are you saying 43?
THE COURT CLERK: Twenty-three.
THE WITNESS: Twenty-three.
Q. Okay. Mr. Goolkasian, are you with me on page 23 now?

A. Yes.
Q. Okay. Now, this is, is it not, the information disclosure statement that Mr. Jones submitted during the prosecution of the '590 patent; correct?
A. Yes, it is.
Q. Okay. And you talked about citation of references to the Patent Office, and you mentioned 37 C.F.R. section 1.97. Do you remember that? That was in the context of submitting references to the Patent Office after a notice of allowance; right?
A. Yes.
Q. Now, that same section of the Code of Federal Regulations, 37 C.F.R. 1.97(h), states that "The filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is or is considered to be material to patentability as defined by section 1.56(b)."
You agree with that; correct?
A. That's correct.
Q. So merely because a reference is cited in an IDS is not an admission that it is material information; correct?
A. Well, it isn't a legal admission, but the question is, why would an attorney cite it unless he believed it was something an examiner would want to know? Otherwise he's just hiding, burying the important references in this

blizzard of paper.

MR. BURWELL: Objection, Your Honor.

THE WITNESS: The IDS does not say --

THE COURT: Wait. Wait. Hold it.

Let me hear the question again.

(Record read)

THE COURT: And the answer?

(Record read)

THE COURT: All right. I'll allow that.

The question is answered.

Next question.

Q. If you look at the first sentence in the IDS, Mr. Jones says: "As a means of complying with the duty of disclosure, Applicants submit a 'List of References Cited By Applicant' on a modified PTO-1449 form and provide a copy of each of the listed references for consideration by the Examiner." Correct?

A. Yes.

Q. And if I can turn your attention to pages 29 and 30 of DTX-2, --

A. Okay. I see that.

Q. -- the references that were identified by Mr. Jones are listed on those pages of the form; is that correct?

A. Yes.

Q. And among those references that Mr. Jones identified

and submitted copies of to the Patent Office were the three references that the examiner ultimately applied as the basis for his rejection in the prosecution of the patent; is that correct?

A. Yes, I believe so.

Q. If I can turn your attention back to page five of DTX-2, and what's then blown up on the screen is a box that says "Searched," with handwritten notes.

This indicates that the examiner made searches of the Patent Office files for art during the course of his examination of this application; correct?

A. Yes.

Q. And the examiner did not locate any additional references beyond those that had been submitted to and by Mr. Jones; correct?

A. I -- I didn't hear all of that question.

MR. BURWELL: Could you read it back, please?

THE COURT: Okay. But we're not going to keep reading back. What you're going to have to do is keep your voice up. Again, I'll say to you what I said to whomever else: If it's easier for you to move your thing over, you're welcome to, but otherwise, keep your voice up so the gentleman can hear you.

MR. BURWELL: Certainly, Your Honor.

THE COURT: You can read that question back,

Chuck.

(Record read)

A. That's correct.

Q. Okay. Let's talk a little bit about the urinary incontinence application.

Now, as some background, you have no familiarity with urinary incontinence, do you?

A. That's correct.

Q. And you don't know what stress incontinence is?

A. Correct.

Q. And you don't know what causes stress incontinence, do you?

A. That's right.

Q. Okay. Now, the '590 patent concerning the use of tomoxetine to treat ADHD is not a continuation application of the '985 application directed to urinary incontinence, is it?

A. No, it's not. It has a different inventor.

Q. And it's not a continuation in part either?

A. That's correct.

Q. And you mentioned that the inventors are different between the ADHD patent and the urinary incontinence patent; correct?

A. Yes.

Q. Now, you mentioned the Board of Appeals opinion in the

urinary incontinence application, and if we could pull up PTX-293, which should be tab five of your binder.

A. I have that. Which particular page is that?

Q. I will direct you to page 76, and focusing your -- I'll wait till you're with me.

A. I have that.

Q. If I can direct your attention to the last paragraph on the page, this is Mr. Jones's appeal brief in the prosecution of the urinary incontinence patent; correct?

A. Yes.

Q. And in this brief, he states that: "Appellant agrees that the Cohen reference draws the link between norepinephrine uptake inhibition and the lower urinary tract. Cohen admittedly makes norepinephrine inhibitors likely urinary tract disorder treatments. Therefore, the examiner is correct in contending that tomoxetine was known as a norepinephrine inhibitor and that norepinephrine inhibitors are known to affect the lower urinary tract and detrussor muscle."

Do you see where I've read?

A. Yes.

Q. And that's because the Cohen reference had reported the effects of nisoxetine on the lower urinary tract; correct?

A. I don't remember the exact chemical that Cohen had

used.

MR. CLEMENT: Your Honor, you know, he didn't let him testify about references before. He's trying to do it on cross.

THE COURT: Yes. I mean, I think we should keep our eye on the ball here. This witness is testifying regarding the inequitable conduct and the activities at the PTO. We seem to be getting into these technical issues that he's already acknowledged no expertise in.

MR. BURWELL: I'll move on, Your Honor.

MR. CLEMENT: Thank you, Your Honor.

BY MR. BURWELL:

Q. If I can direct your attention to page 87 of PTX-293.

Now, this is the opinion that was issued by the Board of Appeals that you testified about on your direct examination; correct?

A. Yes.

Q. Turning to the first paragraph, beginning in the second sentence: "One having ordinary skill in the art would have been taught by the applied references that tomoxetine was known in the prior art to inhibit norepinephrine uptake," citing Zerbe, "and that the inhibition of norepinephrine uptake was known in the prior art to control incontinence, detrussor instability or interstitial cystitis (again, see, for example, Cohen)."

Do you see where I've read?

A. Yes.

Q. And that was the basis for the Board's opinion in the prosecution of the urinary incontinence application; correct?

A. Correct. That, plus the -- the fact that the tomoxetine had less side effects. That was another advantage that they would have seen.

Q. Now, if I can direct your attention back to the prosecution history of the '590 patent, tab one, and specifically, page 27.

A. I have that.

Q. Now, this is from the examiner's first rejection of the claims of the '590 patent; correct?

A. Yes.

Q. And if I can direct your attention -- the examiner has cited the Ryan, the Green, and the Wong references in support of that rejection; correct?

A. Yes.

Q. And I'll turn your attention to the second paragraph. The second sentence reads: "Both Green and Ryan suggest using drugs which are selective inhibitors of monoamine uptake in nerve terminals, such as, fluoxetine to treat (ADHD)."

Do you see where I've read?

A. Yes.
Q. And fluoxetine is not a norepinephrine uptake inhibitor, is it?
MR. CLEMENT: Your Honor, again, I think that's getting technical.
THE COURT: How about it?
THE WITNESS: Do you want the answer?
THE COURT: No. Hold on.
MR. BURWELL: I'll withdraw it.
THE COURT: Yes, I think what we have here is, this is going to be a continuing problem. I'm not going to let him get into all this technical stuff.
MR. BURWELL: I will stay away from the technical stuff, Your Honor.
THE COURT: The technical chemicals.
BY MR. BURWELL:
Q. Okay. Let's go back to the prosecution history of the urinary incontinence patent, PTX-293.
A. Which exhibit is --
Q. I'm sorry. That's tab five of your binder.
A. Tab five. And which page are we looking at?
Q. If I can direct your attention to page 105.
Now, this is a document that you've testified about on your direct examination concerning Mr. Jones's request to withdraw the Board opinion?

A. Yes.
Q. Now, this request was submitted in July of 1994; correct?
A. That's correct.
Q. And the '590 patent application regarding the use of tomoxetine for ADHD was not filed until January of 1995; correct?
A. The -- I'm sorry, could you repeat that question? I didn't -- the numbers are getting me here.
Q. Yes.
The request to withdraw the Board of Appeals opinion in the urinary incontinence case was submitted in July of 1994; correct?
A. Yes.
Q. And then the '590 patent application involving tomoxetine for ADHD wasn't filed until January of 1995; correct?
A. Yes.
Q. Which means that this request for withdrawal of the Board opinion was made over five months prior to the filing of the '590 patent application; isn't that right?
A. Yes. They were still copending, though.
Q. But the request to withdraw the Board opinion was made before any application had even been filed in the '590 patent application; correct?

A. Yes. I don't understand the relevance. I'm sorry.
Q. Let me see if I can simplify it.
The '590 patent application had not been filed at the time that this request to withdraw the Board opinion was made; correct?
A. I understand the fact. I'm just trying to understand the relevance, that's all.
THE COURT: Well, I'll deal with the relevance. Let's --
THE WITNESS: I'm sorry.
THE COURT: Go ahead.
Q. And, in fact, the reason that -- well, let's walk through this request to withdraw the opinion on appeal.
You understand from this document that Mr. Jones had submitted this request because the application that was the subject of the appeal to the Board had actually been abandoned prior to the issuance of the Board opinion; correct?
A. Yes.
Q. And that's because Mr. Jones had submitted a file wrapper continuation of that application before the Board actually issued its opinion; correct?
A. Correct.
Q. And that filing of the file wrapper continuation occurred over a year before the Board issued its opinion;

correct?

A. I didn't check exactly the dates on that.

Q. So the claims that were on appeal to the -- well, let's back up, and I can have you confirm for yourself.

If you go back a few pages to page 96, --

A. I have that.

Q. Do you understand this page to be the first page of the file wrapper continuing application that Mr. Jones filed on May 13th, 1993?

A. Yes.

Q. And that was over a year prior to the Board of Appeals' issuance of its opinion on the appeal; is that correct?

A. That is correct.

Q. If I can direct your attention to page 99, do you recognize this as a preliminary amendment that Mr. Jones submitted in connection with the file wrapper continuation application for the urinary incontinence application?

A. Yes.

Q. And do you see where Mr. Jones canceled claims 7 through 10?

A. Yes.

Q. And do you understand that the claims that were the subject of the appeal before the Board of Appeals included claims 6 through 10? Correct?

A. That's correct.
Q. So some of the claims had no longer -- let me back up.
The file wrapper continuation application acts as an express abandonment of the application, of the parent application; correct?
A. It should, yes.
Q. So the application that was the subject of the appeal to the Board had been abandoned prior to the time the Board issued its opinion on the appeal; correct?
A. Yes.
Q. Okay. Can we go back to page --
MR. CLEMENT: I think the witness was trying to explain his answer.
A. I'm having a little difficulty there. Usually when one files a file wrapper continuation, one says, abandon the previous application, and then one notifies the Board. But that statement isn't in this -- this filing.
Now, it may operate by way of rule, and I didn't check that.
Q. And, indeed, it does operate by way of rule, doesn't it?
A. I'll accept your representation to that.
Q. And it did at the time of the filing of this application. We understand that the terminology and some of the rules have changed in the interim; correct?

A. I'll accept your representation. Correct.
Q. If I can turn your attention back to page 105, this is Mr. Jones's request to withdraw the opinion on appeal? Is that correct?
A. Yes.
Q. This is what you testified about on your direct examination?
A. Yes.
Q. Now, Mr. Jones, does he not, explains the reason for this request to withdraw the opinion. In the second paragraph, he states: "On May 13, 1993, Appellant by his undersigned attorney filed a file wrapper continuation under Rule 62, requesting the express abandonment of the above-titled application as part of the procedure."
And then he attaches Exhibit A of the filing receipts and Exhibit B, the Rule 62 application form.
Do you see where I've read?
A. Yes.
Q. And then if you can turn to the next page, --
A. Yes.
Q. -- looking at the carryover paragraph and the next two paragraphs, Mr. Jones also attaches a copy of the preliminary amendment that he had submitted and says: "Thus, the only claim which is common to the continuation application and to the claims on appeal is claim 6."

"Appellant's attorney inadvertently failed to ask for the withdrawal of the above-titled application from appeal, upon the filing of the Rule 62 continuation. Therefore, the Board's time was wasted in a needless consideration of the case and preparation of the Opinion. The undersigned realizes the significance of his oversight and assures the Board that the error will not be repeated..."

Do you see where I've read?

A. Yes.

Q. So Mr. Jones was apologizing for, in effect, wasting the Board's time; is that correct?

MR. CLEMENT: Your Honor, I think that goes to Mr. Jones's state of mind.

THE COURT: I think it does, and I think that was the subject matter of objections to this --

MR. BURWELL: I'll move on.

Q. Now, as of July of 1994, apart from the application that was pending concerning urinary incontinence, you haven't seen any other evidence of any other applications that had been filed by Lilly concerning uses of tomoxetine; correct?

A. I haven't seen any, other than the two later applications.

Q. And the later application was filed in January of

1995; correct?
A. Yes.
Q. And you haven't seen any evidence that anybody at Lilly as of July of 1994 had contemplated any later applications involving tomoxetine, have you?
A. I have no idea of -- I haven't seen any evidence, and I can't read Lilly's mind.
Q. Now, you submitted a declaration in conjunction with the briefing on a summary judgment motion in this case. Do you recall that?
A. Yes.
Q. And that declaration should be in front of you in another binder, Volume 4.
A. I have that.
Q. And do you recognize this as the declaration that you submitted in conjunction with the briefing on a summary judgment motion in this case?
A. Yes.
Q. That was the summary judgment motion directed to the issue of inequitable conduct; correct?
A. Yes.
Q. And if you would turn to the last page, --
A. Yes.
Q. -- is that your signature there?
A. Yes, it is.

Q. And you declared under penalty of perjury that the foregoing is true and correct; is that right?
A. That's correct.
Q. If I can turn your attention now back to paragraph -- this is on page six. Are you with me on page six?
A. Yes.
Q. In paragraph 25, you're discussing the Board of Appeals opinion that was rendered on July 5th, 1994, and then continuing to paragraph 27, you state: Upon receiving this unfavorable opinion, Jones submitted a file-wrapper continuation application."
Do you see where I've read?
A. Yes.
Q. But as we've just seen, the file wrapper continuation application was actually filed over a year prior to the issuance of the Board's opinion; is that correct?
A. That's correct.
Q. So this paragraph 27 of your declaration is incorrect.
A. It's in error. I didn't check the dates. I apologize.
Q. And when you made this error in your declaration, you weren't intending to deceive the Court in any way, were you?
A. No. The fact of the file wrapper continuation application being filed was correct. The fact of an unfavorable opinion was correct. But the "upon" was not

correct.

Q. So any suggestion that the reason for filing the file wrapper continuation was the subject matter of the opinion is incorrect; is that right?

A. That's correct.

Q. Okay. Let's turn to tandamine.

Now, you mentioned that at some point, Mr. Jones no longer was involved in the prosecution of the '590 patent. You understand that's because he had retired at the end of 1996; correct?

A. I don't know whether he retired or not.

Q. Now, you talked about references that have been cited by the European Patent Office in prosecution of a European counterpart application, and you discussed the MPEP and its discussion of citation of references identified during foreign prosecution.

Now, the MPEP does not require that attorneys indiscriminately submit all Y references that are cited by a foreign Patent Office, does it?

A. Generally speaking, the practice is to submit all Y references. In fact, they submit the entire search report.

Q. But there's --

A. But the rule says or the manual says that it has to be material prior art. The general assumption is is that a Y reference is material.

Q. But if it's not material, then there's no requirement to submit it; correct?
A. That's correct.
Q. Okay. If I could ask you, the slides that we saw during your direct examination; were you involved in putting those slides together?
A. Yes.
Q. And you had put together a timeline. And my copy of the slides are not numbered, but I believe it to be maybe 45 or 46, if we could have that put up on the screen, it's the complete timeline.

Yes, that's the one.

Now, if I can direct your attention to the June 26th, 2000 box, where you state that there was a rejection in the European Patent Office prosecution; do you see that?
A. Yes.
Q. If I can direct your attention to your binder Volume 2, and tab 18, --
A. I'm sorry, you said binder Volume 2 and tab 18?
A. That's correct.
Q. Okay.

Oh, I apologize. I apologize. It should be Volume 3.
A. All right.
Q. I'm sorry.

A. I have that.
Q. Okay. Is this the June 6th, 2000 rejection that you've identified on your timeline?
A. Yes.
Q. Okay. And if I can turn your attention to the second page with the Bates numbers ending in 43.
(Off the record discussion)
Q. While you're finding that, let's take this slide down.
THE COURT: Well, he's got this.
THE WITNESS: I have a page, but --
Q. To give us some context, let's pull up the European search report, which is DTX-211, and the second page of that contains the references identified by the European Patent Office?
A. Yes.
Q. And this tandamine reference is the last one on the list; is that correct?
A. Yes.
Q. Okay. And let's go back to tab 18.
A. I have that.
Q. Plaintiff's Trial Exhibit 914.
A. Yes.
Q. Now, on the second page, in paragraph one, the European Patent Office is saying -- this is a document you considered in your work on this matter; correct?

A. Yes.
Q. And you understand that the tandamine reference was identified as D-4 by the European Patent Office?
A. Correct.
Q. And you understand that the European Patent Office was using T as an abbreviation for tomoxetine?
A. Yes.
Q. And here, the European Patent Office is saying: "Since tomoxetine is a norepinephrine reuptake inhibitor, the teaching of D3 and D4 directed to SRI cannot be taken into consideration." Correct?
A. Correct.
Q. So this is not a rejection over the tandamine reference; correct?
A. The -- I think -- you may be right there. Correct.
Q. Now, in fact, there was a previous rejection by the European Patent Office; correct?
A. Could you point me to that?
Q. I'm going to have to ask you to move to another binder. It's binder 1, tab two, and this is DTX-215.
THE COURT: It's on the screen. It may be easier for you to deal with that, because that witness chair is -- the witness area is small.
Q. Let's turn to the second page -- I'm sorry, the third page, and if we can blow up the screen beginning with

paragraph three.

Here, the European Patent Office is saying: "According to D3 -- " -- which was another reference -- " -- a serotonin reuptake inhibitor (hereinafter referred to as SRI), is effective in the treatment of ADHD."

Do you see where I've read?

A. Yes.

Q. And then in the last sentence, the European Patent Office examiner says: "Likewise, tandamin, another SRI, has been reported to be effective in the treatment of ADHD as well." Correct?

A. Yes.

Q. But tandamine was not reported to be an SRI, was it?

A. That's correct.

MR. CLEMENT: Objection, Your Honor. I think this is getting technical again.

THE COURT: Yes. Again, we're back to where you've having him testify now as a chemist.

BY MR. BURWELL:

Q. Do you -- you assert that the tandamine reference was material to the patentability of the '590 patent; correct?

A. I assert it's material because it was a Y reference, and an examiner may have found something in there that he wanted to know about.

Q. So you're not relying on the content of the reference

itself.
A. No, other than -- there is content in there, but I'm not sufficiently skilled to be able to pick it out.
Q. If I can turn your attention to tab 17 of your binder, PTX-913, and we can blow this up on the screen as well.
THE COURT: If he doesn't have to use the binders I'd like him --
MR. BURWELL: Okay.
THE COURT: -- only because he's in a very cramped space there, and it's very difficult to use them.
MR. BURWELL: I'll try to direct these to be blown up on the screen.
THE COURT: Yes, if you have the ability to put them up, technology be faster.
Q. If we can call up the first paragraph.
Now, do you recognize this as the response by Lilly to the European Patent Office's June 6th rejection?
A. Yes.
Q. If I can turn your attention to the second page, the second full paragraph, beginning five lines from the bottom of that paragraph, there's a sentence that starts: "The Applicants believe that D4 -- " -- which you understand is the tandamine reference -- " -- is not particularly relevant to the patentability of the present invention, claiming the use of a structurally distinct compound, for use in the

manufacturing of a medicament which is useful for treating a wholly different disease state than that disclosed by the" tandamine reference.

Do you see where I've read?

A. Yes.

Q. And then they go on to state: "The Applicants cannot locate the teachings in reference to D4 that suggest to the artisan that tandamine is effective for treating ADHD." Do you see that? Do you see where I've read?

A. Yes.

Q. And then going to tab 18, PTX 914, if we can blow that up on the screen, this is the European Patent Office document that you had discussed in your time line, and on the second page, we see the European Patent Office states, as we saw before -- if you blow up the first paragraph -- "The use for tomoxetine in the treatment of ADHD could not have been derived from any of D1 through D4, alone or in combination."

Do you see where I've read?

A. Yes.

Q. Okay. Now, you talked about Mr. Titus's submission of European -- references cited in European search reports in other patent prosecutions before the U. S. Patent Office.

A. Yes.

Q. If I can direct your attention to PTX-300, which is at

tab six of your binder, this is one of the prosecution histories that you identified as one where Mr. Titus had submitted references that had been cited in a European Patent Office search report after issuance of a notice of allowance; correct?

A. That's correct.

Q. If I can turn your attention to page 81, and this is a document showing that Mr. Titus submitted references cited by the European Patent Office on July 24, 1999; is that correct?

A. Yes.

Q. And turning to page 84, this is the European search report that lists the references that Mr. Titus submitted in this instance; is that correct?

A. That's correct.

Q. And the tandamine reference is not listed on this European search report, is it?

A. That's correct.

Q. And Mr. Titus did not submit the tandamine reference to the Patent Office in connection with this application, did he?

A. That's correct.

Q. Okay. If I can direct your attention now --

A. He didn't cite it.

Q. -- to PTX-301.

A. PTX-301.

Q. Tab seven of your binder.

Turning your attention to page 70, -- oh, I'm sorry. Let me take you back to the first page of this document.

This is the prosecution history of the patent application directed to the use of tomoxetine to treat oppositional defiant disorder that you discussed in your direct examination as another instance in which Mr. Titus had submitted references cited by the European Patent Office to the U. S. Patent Office. Do you understand that?

A. That's correct.

Q. If I can turn your attention to page 70, --

A. Yes.

Q. -- this is the information disclosure statement that was submitted by Mr. Titus, and it shows it was submitted on July 15, 1999. Do you see that?

A. Yes.

Q. If I can turn your attention to page 73, this is the European search report that lists the references that were cited by Mr. Titus to the Patent Office in this application; correct?

A. Yes.

Q. And the tandamine reference is not listed on this European search report, is it?

A. That's correct, it's not cited.
Q. And if you notice, all of the references that are listed on this European search report are X references; is that correct?
A. Yes.
Q. And just to close the loop on the previous document we looked at, going back to PTX-300 at page 84, this is the conduct disorder patent application, and again, all of the references cited by Mr. Titus that had been identified in the European search report were X references; is that correct?
A. That's correct.
Q. And what is an X reference?
A. An X reference is a reference that by itself would make the subject matter obvious or unpatentable.
Q. Can we scroll down to the bottom of the form?
The identification of the letters used to describe references is down at the bottom, and you agree that an X reference is one that the European Patent Office considers particularly relevant if taken alone; correct?
A. Correct.
Q. Let's go back to your declaration submitted in connection with the summary judgment briefing. That's Volume 4, tab number 2.
If I can direct your attention to paragraph 48,

located on page nine.
A. Yes.
Q. Actually, let's go back to paragraph 47 and 48 and show those together.
In this part of your declaration, you are talking about how Mr. Titus had received the corresponding European search reports in the counterpart to the '590 application; correct?
A. Yes.
Q. And then in paragraph 48, you say you also understand from Mr. Titus's deposition testimony that on prior occasions when he had received European search reports on other applications to atomoxetine, he had removed the applications from allowance in order to cite the European search report.
Do you see that?
A. Yes.
Q. But as we've just seen, the evidence that you've cited did not occur on prior occasions, it was on subsequent occasions; correct?
A. That's correct. The paragraph said it's my understanding, and we're not testifying in court to that, it was on prior occasions.
Q. I'm sorry, I didn't hear the last part.
A. It says it was my understanding, and it was my

understanding at that time, but when we were making the timelines realized that's not the case, and so we changed it.

Q. Okay. So your understanding was incorrect at the time you made this declaration.

A. That's correct.

Q. Okay. If we can turn to tab 14, which is in binder three, it is PTX-770, and page 944381.

Now, this is a document that you talked about on your direct examination where Mr. Titus had submitted the European search report that had been issued by the European Patent Office in the ADHD prosecution -- prosecution of the European counterpart to the ADHD patent. This is Mr. Titus's submission -- well, this is the submission of the search report to the Canadian Patent Office; correct?

A. Yes.

Q. If we can turn to page 944369, and the text at the bottom right-hand portion of the page states that, in the third paragraph: "It would be to an applicant's advantage to furnish particulars of the prior art cited in respect of the corresponding applications before the United States Patent Office and European Patent Office when such information becomes available. Furthermore, in order to assist in the examination of this application, a copy of all non-patent citations would be appreciated."

Do you see where I've read?

A. Yes.

Q. And do you understand that Mr. Titus testified in his deposition that he cited the European Patent Office search reports to the Canadian Patent Office because of this request by the Canadian Patent Office?

A. This says to his advantage, they would like to have that, and it's the same thing the United States Patent Office says. Now we're treating the European patent -- the Canadian Patent Office with deference, and we're saying to the United States Patent Office we're not going to send you that, we're not even going to explain why we're not sending it to you.

Q. Do you understand that Mr. Titus had testified that it was submitted to the Canadian Patent Office as a matter of course?

A. As a matter of what?

Q. As a matter of course?

A. As a matter of course? He submits -- submitted the other references that were foreign search reports as a matter of course, but somehow he didn't send it, this one particular one, to the U. S. Patent Office as a matter of course. That's all it would have taken, to just submit it.

MR. BURWELL: Your Honor, one moment while I confer?

THE COURT: Yes.

MR. BURWELL: Your Honor, would now be a good time to break for lunch.

THE COURT: Where do you stand with respect to your questioning?

MR. BURWELL: My colleagues would like to suggest a few additional questions.

THE COURT: Is it going to be much in the way of redirect?

MR. CLEMENT: I don't think I have anything, Your Honor, so far.

THE COURT: How many more questions do you have? Do you need time?

MR. LIPSEY: I was going to suggest, if possible, if we could take a moment to confer over lunch, we're probably done, or very close to it, I would think.

THE COURT: All right. My problem is, is this witness going to be staying around?

MR. CLEMENT: I think he's scheduled to leave today.

MR. LIPSEY: I mean, if he's going to be excused with no redirect, I would not ask him to stay.

THE COURT: We shouldn't keep the witness hanging around if he's not otherwise going to have to be here if it's just a matter of a few more questions.

MR. LIPSEY: If they represent there is no redirect, as a courtesy to Mr. Goolkasian, I'll --

THE COURT: I just want the record to be clear I'm not precluding you from asking more questions, but I'm trying to be, you know, aware of people's time.

MR. CLEMENT: We have no redirect.

THE COURT: Well, you've got that.

MR. LIPSEY: Then we're done, too, Your Honor.

MR. BURWELL: Then no further questions.

THE COURT: Look at that. Look at what I've saved you.

(Laughter)

THE COURT: Can the witness step down?

MR. BURWELL: Yes.

THE COURT: You're done, sir. Thank you very much.

Go ahead. Do you want to move exhibits into evidence? In the normal circumstances, this would go in in your case, but I guess there's no objection about evidence going in on whomever's case, correct?

MR. CLEMENT: We don't have any objection to that, Your Honor.

THE COURT: All right. Go ahead.

MR. BURWELL: I would like to move into evidence Plaintiff's Exhibit 913, Plaintiff's Exhibit 914,

Defendants' Exhibit 215, and Plaintiff's Exhibit 912, if it was not already mentioned.

THE COURT: Any objection?

MR. CLEMENT: Can we have a representation those are the ones we saw during the testimony?

MR. BURWELL: That's correct.

MR. CLEMENT: No objection.

THE COURT: Into evidence.

(Plaintiff's Trial Exhibits 912, 913 and 915 and Defendants' Trial Exhibit 215 marked in evidence)

THE COURT: Anything else?

MR. BURWELL: That's all, Your Honor. Thank you.

THE COURT: You may step down, sir.

THE COURT: Which witness do we have next?

MR. PARKER: Dr. James Johnson, Your Honor.

THE COURT: And the witness is here?

MR. PARKER: He is, Your Honor.

THE COURT: All right. As I told you, we're going to go until 3:30 today.

MR. PARKER: That's correct, Your Honor.

THE COURT: All right. It's about quarter after 12. We'll see you back here at quarter after one.

MR. PARKER: Thank you, Your Honor.

THE COURT: Thank you.

(Luncheon recess taken)

A F T E R N O O N S E S S I O N

THE COURT: Be seated.

There's been a slight change in my schedule. We're going to go to six today --

(Laughter)

THE COURT: We're going to break at three, not 3:30. Okay?

Next witness.

MR. PARKER: Thank you, Your Honor.

Your Honor, my name is Tom Parker. I'm here for the Defendants.

Mr. Clement would like to address the Court.

MR. CLEMENT: I forgot yesterday to introduce My colleague, Dr. Andrea Wayda, who is going to be seated at counsel table for this witness.

THE COURT: All right. Fine.

MR. PARKER: Your Honor, Defendant calls as its next witness Dr. James Johnson.

MR. LIPSEY: And, Your Honor, the witness will be handled on our end by my partner, Mr. Bajefsky.

THE COURT: Fine.

Up here, sir.

MR. PARKER: Your Honor, may we provide you with the witness binders at this time?

THE COURT: Sure.

THE COURT CLERK: Placing your left hand on the bible, raising your right hand:

J A M E S R O B E R T J O H N S O N, called as a witness on behalf of the Defendants, and having been duly sworn, testified as follows:

THE COURT CLERK: Please be seated.

Please state your name, spelling it for the record.

THE WITNESS: My names is James Robert Johnson, J-a-m-e-s, R-o-b-e-r-t, Johnson, J-o-h-n-s-o-n.

DIRECT EXAMINATION

BY MR. PARKER:

Q. Dr. Johnson, would you just please state your name and address for the record, please?

A. James Robert Johnson, 2129 East Glen Alden Drive, German town, Tennessee, 38139.

Q. Now, Dr. Johnson, you have been retained by Defendants as an expert in this case?

A. Yes.

Q. Dr. Johnson, you've been practicing in the area of pharmaceutical dosage form development and drug delivery system development for over 40 years. Is that fair?

A. Yes.

Q. Dr. Johnson, do you have your CV in front of you? I'd like you to just have that handy because I'd like to go over

your background.

A. Okay.

MR. PARKER: Your Honor, may I just approach the Court with two copies of the CV?

THE COURT: Sure.

Q. Dr. Johnson, can you just briefly tell us a little bit about your educational background?

A. Yes. I have a B.S. in pharmacy from the University of Minnesota in 1962, and I have a Master's and a Ph.D. in pharmaceutics at the University of Minnesota College of Pharmacy with a minor in physical chemistry.

Q. I'm sorry, did you mention a Master of Science in pharmaceutics from the University of Minnesota?

A. Yes.

Q. And when did you receive that degree?

A. 1968.

Q. Now, by whom are you currently employed?

A. University of Tennessee College of Pharmacy.

Q. And what position do you hold at the University of Tennessee?

A. I'm associate professor.

Q. And how long have you had that position?

A. I've been working with the University of Tennessee for approximately 25 years. For the first 10, I was a volunteer, where I had developed some courses and worked

with graduate students and was on thesis committees, and then for the last 15 years, I've been an employee, employed as associate professor.

Q. Now, are you currently doing any research at the University of Tennessee?

A. We're doing a variety of things. We have six graduate students. We have a visiting colleague from FDA in China who's going to be with us for a year who's going to be working on dosage forms and raw materials. We have a research associate, and we have an instructor that I work with, and we've recently added two more -- an assistant professor that's going to work with our group, and we've added two more students.

Q. Dr. Johnson, are you doing any research on injectable sustained-release dosage forms?

A. We've worked on injectable sustained-release -- depot research -- research on depot systems since approximately 1992.

Q. Are you also conducting research on development of soluble systems for high-dose drugs?

A. Yes.

Q. And could you just briefly explain just generally?

A. These high-dose drugs are becoming increasingly important because many of the new drugs are even more insoluble than some of the old ones, so what we've been

doing is trying to find new ways to solubilize these and then put them in a format where you can easily use these to formulate either tablets or other dosage forms.

Q. Now, Dr. Johnson, do you do any teaching at the University of Tennessee?

A. Please repeat.

Q. Do you do any teaching at the University of Tennessee?

A. Yes. Over the last 15 years, I taught in the parenteral drug development course, and I've also lectured in a preformulation course that we offer, and we've also developed a tableting course that we've taught 34 times in the last 12 years to more than a thousand people.

Q. Do you teach any courses concerning injectable drugs?

A. Pardon me?

Q. Have you taught any courses --

A. Yeah, I've taught in the parenteral drug course.

Q. All right. Now, you just mentioned something about a tablet course. Could you just tell us a little bit about that?

A. It's a course that we offer to industry people three times a year, and we offer it to the graduate students and we offer it to the pharmacy students, and it -- it really tries to prepare people who may be entering the area about preformulation, formulation, granulation, tableting, coating, and analytical support and review of what else you

might do to evaluate the products.

Q. Thank you, Dr. Johnson.

Now, let's just talk a little bit now about your experience in the industry.

Can you please tell us about your most recent industry employment?

A. Most recent was Schering-Plough.

Q. And you were there from what period of time?

A. From 1976 to 1996.

Q. And did you hold various positions at Schering-Plough?

A. I had held various positions. I started as a manager in '76 and held various positions. The last 14 years, I was vice president of R & D in one area or another.

Q. And were you also -- I believe you were vice president of R & D development for the pharmaceutical and I believe sun care groups.

A. It was -- we managed the development of over the counter drug products, the sun care products, and the Dr. Scholl products.

Q. Were you also vice president of the new technologies group?

A. Yes.

Q. AND what was that? Can you tell us a little bit about that?

A. We explored a variety of new technologies to try to

determine if we could find delivery systems which would be appropriate for our products.

Q. Now, just how long were you at Schering-Plough, again?

A. Twenty years.

Q. Twenty years?

A. Twenty.

Q. And what types of drug development work did you do at Schering-Plough?

A. We -- in the pharmaceutical area, we developed all kinds of dosage forms, including suspensions, tablets, coated gums, aerosols, various types of products. And --

Q. So were you employed in any preformulation work?

A. Yes, I had a preformulation group.

Q. And can you just define for us, for the Court, what do you mean by preformulation?

A. This is where we typically try to examine the characteristics of the drug substance and compatibility that it would have in various systems, in either solvent systems or aqueous systems.

Q. Did you oversee the formulation group?

A. Yeah, I had at least three or four formulation groups at various times. We generally divided these into expertise in tablets, liquids, topical products, aerosols.

Q. And what's the difference between -- you described preformulation. What did you mean by formulation group?

What did they do?
A. The formulation group is where we were actually putting the drug in a dosage form which we can either test or utilize in some way.
Q. Now, during your tenure at Schering-Plough, I believe you described, and correct me if I'm wrong, that basically, you have the responsibility of giving the quote-unquote green light with respect to the -- before any product was launched at Schering. Can you just describe what that responsibility entailed?
A. For -- it's probably over 10 years, but what we did is, we would -- before we would approve any product for release, we would put together all the data in a binder and we would compile all of our preformulation work, our formulation work, our analytical work, our safety work, our tests, any clinical testing work we might have done and stability work, and I'd review that and make a determination whether we had completed all the work necessary.
Q. Now, did Schering-Plough also look to you for expertise in terms of -- with respect to just drug development in terms of what would be involved, what would be needed, the cost, expenses, resources, things of that nature?
A. Yes, I would typically be involved pretty early in the process to try to estimate how long it would take us to

complete projects, the amount of effort it would require, the complexity it would require.

Q. Now, prior to your employment at Schering-Plough, did you have any other industry experience?

A. I worked at Ayerst Laboratories for eight years.

Q. And can you just tell us what titles you held at that company?

A. I was senior pharmacist, group leader, section head.

Q. And, I'm sorry, were you section head of the pharmaceutical development group?

A. It was pretty much the solids group, where we did the solid formulations, the standard release formulations and suspensions. We also looked at some other liquid systems, but it was basically those dosage forms.

Q. And so what were the years that you were employed by I believe it's Ayerst?

A. '68 to '76.

Q. So approximately how many years of industry experience do you have in drug development?

A. Twenty-eight.

Q. And were those years directed primarily to developing various dosage forms?

A. Yes.

Q. Do they involve pharmaceutical drugs?

A. Yes.

Q. Now, have you ever served as a consultant, and if you did, can you briefly describe the activities you have undertaken as a consultant?

A. We served periodically as a consultant to various companies who called, and we'd conduct projects for them. We're currently working on a sustained-release project for a company. We have done delivery-system products which were also delayed or time-release for oral use, like bypass the stomach and were selectively for release in the intestine, and various projects like that.

I've also been principal investigator for six small business grants that -- I think five were NIH, one was FDA.

Q. And can you just tell us what was the nature of those -- what was the subject matter --

A. They were various things. One was a tableting project. We made tablets, capsules -- or not capsules, it would be tablets in a solution, and a chewable tablet.

Another one was where we -- in fact, three of them were a sustained-release depot injection project. Another one was a sustained-release injection product for opiate addiction. We've also done a variety of other projects in opiate addiction. We've developed several systems which are very difficult to abuse. We're looking for abuse, drug-abuse-resistant systems.

Q. Now, Dr. Johnson, are you a member of any scientific societies?

A. The American association of Pharmaceutical Sciences and the Controlled Release Society.

Q. Now, given the number of years you have in the industry -- you've had in the industry and also in academia, do you consider yourself a person having substantial knowledge about the various disciplines required to develop a pharmaceutical dosage form and the amount of time, resources and efforts necessary for formulating those dosage forms?

A. Yes.

Q. Now, again, Dr. Johnson, based upon all your years of experience in the industry and academia, do you consider yourself a person who is highly knowledgeable about immediate and controlled-release drug delivery systems?

A. Yes.

Q. Tablets?

A. Yes.

Q. Oral solutions?

A. Yes.

Q. Suspensions?

A. Yes.

Q. Injectable solutions?

A. Yes.

Q. Depot injections?
A. Yes.
Q. Suppositories?
A. Yes.
Q. Topical drug delivery systems?
A. Yes.
Q. And I'm sure they are others, but those -- are there others as well that I have not mentioned? You don't have to mention them. Just, are there others?
A. There probably are. We did an awful lot of different dosage forms.
Q. Now, you used the word "pharmaceutics" I believe in connection with your experience. What is pharmaceutics? What does that mean?
A. When I took it, it meant, it was basically application of physical chemistry to pharmaceutical dosage systems.
Q. Now, in your experiences, Dr. Johnson, did you have an occasion to work with physicians in terms with respect to drug development?
A. Yes, most of our products were tested in some way or another. We did -- I had a small group, which we'd do a lot of the topical evaluations and testing, and then we generally worked with various physicians for other testing.
Q. And did you have an occasion to work with clinicians?
A. Yes.

Q. Any others in other disciplines that you had to interact with?

A. I actually worked with quite a few of the Schering people in both their chemistry, their legal department, and other areas.

Q. Now, while you were at Schering, were you responsible for overseeing technical disciplines, and, if so, can you please describe the groups that you were responsible for overseeing?

A. Well, over the years, I managed a number of groups. When I started, I believe I had approximately 10 people. We were basically a formulation group, and a stability group, and I think we had the packaging group, and then eventually it grew to roughly 100, 110 people, where I was managing virtually all aspects of the drug development except the FDA interactions and the clinical department.

Q. All right. Were you also responsible for overseeing the physical pharmacy group at Schering-Plough?

A. Yes. I had a physical pharmacy group -- well, we called it that for a while, then I think we changed the name to preformulation. That I had a variety of preformulation groups in solids, liquids, topical products, aerosols.

Q. Did that group have any responsibilities with respect to characterizing various dosage forms?

A. Well, they would prepare the dosage forms and then

they would develop test techniques to allow us to characterize them and test them.

Q. Now, have you yourself participated in any clinical studies of animals and humans?

A. Yes, we currently did a rather large number of samples last year in rats with buphenophrine depot injections.

Q. And in your years of experience, do you have any participation -- we know you're not a physician, but did you have any involvement or participation in connection with human studies, any development of a dosage form?

A. We would be involved in the design of a number of these studies, especially for topical evaluation. We were involved in let's say start-up, trying to figure out how you would go about testing sustained-release systems.

MR. PARKER: Your Honor, at this time, Defendants would like to tender Dr. Johnson as an expert in the field of pharmaceutical dosage form development and drug delivery system development.

THE COURT: Any objection?

MR. BAJEFSKY: No, Your Honor.

THE COURT: He may so testify as an expert.

MR. PARKER: Thank you, Your Honor.

BY MR. PARKER:

Q. Now, Dr. Johnson, did Defendants ask you to provide an opinion -- let me strike that.

Did Defendants ask you to provide any opinions on any issues relating to this case?
A. Yes.
Q. And what was that issue?
A. I was asked to give an opinion on whether one of ordinary skill in the art could complete the claims of the '590 patent without undue experimentation.
Q. Now, in rendering and reaching that opinion or conclusion, did you review or rely on any materials?
A. Yes.
Q. And can you just -- what materials did you rely on?
A. I looked at the '590 patent, some early -- early patents relating to formulations and some of the chemistry. I also looked at some supporting publications. I looked at some literature references. And I also used my own opinion.
Q. I'm sorry, what was that?
A. I also used my own opinion based on my experience.
Q. Now, in making this assessment with respect to undue experimentation, did you consider a series of factors?
A. I considered the Wands factors.
Q. Well, us lawyers call them the Wands factors. I understand you're familiar with that. But which factors do they entail?
A. They entail the nature of the invention, the breadth of the claim, relative skill in the art, the amount of

guidance disclosed by the patent, the presence or absence of working examples, the predictability of the art, the quantity of the experimentation necessary, and the state of the prior art.

Q. All right. So in reaching your opinion which you'll provide later on, these were the factors that you considered in doing so?

A. Yes.

Q. Now, you mentioned the date January 11th, 1995. What is the significance of that date?

A. That's the date of submission of this '590 patent.

Q. And what role, if any, did that date play in your analysis?

A. I tried to evaluate it these factors based on what was the technology at that or prior to that date.

Q. Okay, Dr. Johnson. Let's look at the first Wands factor, which is the nature of the invention.

Now, you testified just before that you considered all the Wands factors, so let's turn to the nature of the invention.

And what conclusions did you reach with respect to that factor?

A. I tried to determine what is the nature of events. To me, it meant that it was the method of -- I tried to determine the nature of the invention by -- and to me, it

meant that it was a method of treating ADHD by administering an effective amount of atomoxetine to a patient in need of the treatment.

Q. And did you also consider to any extent the methods of administration of atomoxetine?

A. Yes. I reviewed the patent and tried to determine the theory and examples or any other information or instruction for how it would be administered.

Q. Now, with respect to ADHD, do you have an understanding of or did you have -- did you consider the manner in which ADHD is treated?

A. Yes. It's known to be a chronic disorder, and it requires extensive treatment for more than -- like probably four to six weeks to determine efficacy, and that makes determining whether or not a product is active much more difficult.

Q. Now, with respect to this factor, the nature of the invention, did that have any effect in your ultimate conclusion?

A. Yes. It made -- to me, it means that the product is more difficult to complete, and undue experimentation is likely.

Q. Now, in your analysis, Dr. Johnson, did you consider the breadth of the claims of the '590 patent?

A. Yes.

Q. And what conclusions, if any, did you reach in that connection, in that regard?

A. Well, claim 1 is very broad, and it's a method of treating attention deficit/hyperactivity disorder comprising administering to a patient in need of such treatment an effective amount of atomoxetine.

Claims 2 to 16 depart from this and depend upon this, and they are generally there to narrow the claim.

But the scope is very broad as to dosage forms they might utilize in administering atomoxetine.

Q. Dr. Johnson, if you would just speak up a little louder.

A. I don't know if I can. I can move the chair.

Q. All right. Thank you.

What do you mean by that you felt that the claims were very broad? And I'm speaking with respect to claims 1 through 16. Is that what you meant, they were very broad?

A. Yes.

Q. Okay. What did you mean by they were very broad?

A. They don't really specify a dosage form that you have to use and they really allow any -- any sort of dosage form to be used, and I just think that expands the scope.

Q. Did you consider whether or not the claims place any limitation on the form of atomoxetine?

A. I don't see -- I didn't see any limitation on those

claims.

Q. Now, is there anything in the specification that you -- when you reviewed the patent, was there any language in there that played a role or part in your analysis of the breadth of the claims?

A. Yes.

Q. And can you refer to that? You can see it on your screen or up on the slide.

A. Yes, those are the -- they really first talk about all pharmaceutical forms, such as tablets, capsules, suspensions and the like, and that's one route of administration. Then they also talk about other types of forms, such as injectable solutions, depots and suppositories and the like. And these are dosage forms that really are not orally administered, and absorption amounts are quite different.

Q. Well, let me ask you, did you consider the phrase at all "and the like"? Did that have any meaning to you? Did that have any significance to your evaluation of the scope of the claim?

A. Yes.

Q. What was that?

A. It indicated to me that they really weren't limiting the dosage forms to tablets, capsules or suspensions for oral use, or they were not limiting those other ones mentioned on the slide with regard to dosage form.

Q. Okay. And where in the patent is that located? Is that referred to in the slide there? Can you identify where that is located?

A. That's in the '590 patent, column 2, lines 28 to 30.

Q. Now you mentioned that -- I believe you were referring to, with respect to the language we were just referring to in the patent that that was broken or that came -- that identified pharmaceutical dosage forms into two categories?

A. Yes, we had oral, and then we have non-oral.

Q. And what's the difference between the two?

A. The difference is in the -- one of the main differences is the impact in dosage. When the drug would pass through the mouth, stomach and liver, it may be subject to the first-pass effect, and indeed, with this drug, it is. So the problem with this drug happens to be that there's extensive metabolizers and there's slow metabolizers. So dosing is not simple.

With the non-oral dosage forms, the depot injections pass through tissue into the bloodstream. Transdermals pass through the tissues into the bloodstream. Suppositories pass through the mucosa of the rectum into the blood steam. Injectables introduce directly into the bloodstream. So what we don't know is, we don't know what the dose would be for these non-oral dosage forms. We have no reference point as to treatment of any individual with

these dosage forms.

Q. All right. Now, when you say we don't know, what are you referring to?

A. We don't know -- we don't know the dose that would be administered.

Q. The specification doesn't provide that for you?

A. No.

Q. Now, just staying with the scope, the breadth of the claims, Dr. Johnson, just to give us a sense -- well, let me back up.

You mentioned extensive metabolizers and poor metabolizers of atomoxetine; do you recall that?

A. Yes.

Q. Can you just generally explain what that means?

A. That means that the blood levels for people who metabolize slow versus fast will have --

MR. BAJEFSKY: Objection, Your Honor. He's talking about clinical issues, and he is not competent to testify about those issues.

MR. PARKER: Your Honor, the whole issue about extensive metabolizers and poor metabolizers, that's in the references that he considered and that he relied upon. He certainly is competent to understand the -- he didn't actually conduct the studies, he wasn't a clinician, but he understands the data that was generated and the conclusions

that were drawn in that particular paper.

THE COURT: I think that was part of the issue of the in limine motion also as to whether or not he conducted this.

I'm going to allow him to testify.

BY MR. PARKER:

Q. Just generally, based on your understanding of the literature, what did you understand extensive metabolizers and poor metabolizers to mean?

A. It means that the blood levels will vary widely between these two groups.

Q. How widely were they between the two groups?

A. Half-life was like four and a half hours with the fast metabolizers and up to around 17, 18 with the slow. But this is a very important factor to consider when you're making any kind of delayed-release formula or sustained-release formula.

Q. So for us lay people to understand, so basically, poor metabolizers would just have it in their system, the drug, a lot longer than the extensive metabolizers. Is that fair?

A. Say that again.

Q. So just to kind of put it into lay language, that the poor metabolizers, the difference between poor metabolizers and extensive metabolizers with atomoxetine is that the poor metabolizers just have the drug in their system for a longer

period of time.
A. The half-life is about 17 hours to let's say go from 100 to 50, if that would happen to be the blood level.
Q. Now, just staying on the scope of the claim, the breadth of the claim, okay, did you give considerations of the types of dosage forms that could fall within the scope of that -- of claims 1 through 16 of the '590 patent?
A. Yes, this is a list of representative dosage forms that we considered, and includes sustained release solutions, suspensions, fine granules, orally disintegrating tablets, sustained-release oral tablets, sustained-release oral capsules, depot injections, transdermal delivery systems, thin films, injectable solutions, delayed-release tablets and capsules, delayed-release and sustained-release tablets and capsules where you would coat the matrix, and chewable, could be chewable tablets or chewy, gooey tablets that you might make for children.
Q. All right. We'll be going over some of these in some detail, but where did you get this list? I'm sorry, where did you get some of these dosage forms?
A. This was abstracted from -- we took this from the Lilly list of line extensions.
Q. Now, was that Exhibit DT -- Defendants' Exhibit 162 in your binder?
A. Yes.

MR. BAJEFSKY: Your Honor, we object to the use of this document and any testimony based on it. It was, in fact, cited in his expert report for a single purpose, and that is that the atomoxetine had a bitter taste. It is nowhere else mentioned in his report. He does not rely on it any place in his report as part of his opinion, and when he raised it on his own in the deposition, in his deposition, I asked him what he knew about it, and he didn't know anything about it. He said he was guessing what it was and he had no factual basis for any of the testimony that he was giving.

MR. PARKER: That's absolutely not true. He testified for about a half hour on this document during his deposition. He gave an extensive discussion exactly about what it meant. I mean, he was in the industry for 30 years. He knew exactly what this document was. It's a line extension document. Lilly considered a whole slew of various dosage forms.

Now, it was also, Your Honor, listed as materials that he reviewed and relied upon, discussed at his deposition, and it was cited in his deposition, and he was deposed on it.

THE COURT: Let me see the part in the deposition that you say where he says he doesn't know anything about it.

MR. BAJEFSKY: Okay.

Can we bring it up?

Page 247.

THE COURT: And hand me a copy of the deposition.

MR. BAJEFSKY: Okay.

If we start at page 247, Your Honor, and his answer beginning on line 11.

THE COURT: Yes, let me just review this.

Chuck, let me have the basis to counsel's objection read back.

(Record read)

THE COURT: And is it your position that in support of the claim that he didn't know anything about it, he was guessing about it is that which is contained --

MR. BAJEFSKY: Well it's on 248.

THE COURT: I'm reading -- is that which is contained in pages 247 and 248?

MR. BAJEFSKY: 247 and 248, and then on 254.

THE COURT: Hold on.

Now, I'm going to allow him to testify. I don't think that the deposition that I just read supports that objection, and I think under these circumstances, too, he uses the words, I guess with this, I guess with that. But I think that this goes to the weight of the testimony and not the admissibility.

I'll allow it. Let's go.

MR. BAJEFSKY: Your Honor, one other point, if I may make one other point on it.

THE COURT: Okay, but usually, once I rule, that means we stop and we move forward. I don't go back and re-rule.

What is it?

MR. BAJEFSKY: This is a 2007 document. He said his opinion was based on what happened in 1995. This has nothing to do with the state of the art in 1995, Your Honor.

THE COURT: What do you say to that?

MR. PARKER: Well, Your Honor, in their brief, Lilly says at about -- well, Plaintiffs say: "There is no evidence that atomoxetine or its salts has any chemical or physical characteristics that would present any special problem in formulating dosage."

This document is inundated with statements that contradict that position.

Now, the fact that they're saying now in a 2006 document about all these technical issues with respect to tomoxetine, they also were present, they had to have been present in 1995. So -- and right now, as part of Dr. Johnson's testimony right now, he's simply looking at this document, saying, look, Lilly assessed at least these dosage forms, using these as examples what is in the scope

of the claims.

THE COURT: I'm going to allow it. I'm going to allow it. And there's no jury here. If after cross-examination or otherwise it can be demonstrated to me that this would be inappropriate, I always have the opportunity to reject it.

Okay. Let's go.

BY MR. PARKER:

Q. Okay. So, Dr. Johnson, so again, we're on the breadth of the claims, and what you have presented in slide eight, which is various dosage forms, these dosage forms are the ones that you feel fall within the scope of the claims of the '590 patent?

A. Yes.

Q. And these were dosage forms that you extracted from Lilly document DXT-162?

A. Yes.

Q. We have lots to cover, but you mentioned first-pass effect. Could you just tell us what that means? Just generally.

A. Generally, what it means is, when the drug is taken orally, it has to be dissolved, and then it will pass through the stomach, intestine, and the liver will metabolize it.

Q. Now, is there an example of a dosage form that would

not have first-pass effect?
A. Dosage forms which are let's say topically or rectally or injected directly into the blood. The depot injections won't be affected in that manner.
Q. Now, Dr. Johnson, with respect to DTX-162, is this where you were able to obtain the list of dosage forms?
A. Yes.
Q. And I'm referring to STPAT 769571.
All right. Now, are there other dosage forms that you feel also fall within the scope of the claim of the '590 patent?
A. We looked at a couple more here where we thought that you possibly could do sublingual tablets, you could do lozenges, ointments, or other topical systems, or you could do other liquids, like elixirs.
Q. Now, these dosage forms existed in 1995, did they not?
A. Yes.
Q. And what about these dosage forms?
A. Yes.
Q. Now, you talked about --
THE COURT: You know, you're saying "these dosage forms." I don't know what this is going to look like on the record. Nobody's going to know what "these dosage forms" are. I think we're going to have to -- I'm certainly not going to remember.

Q. With respect to the dosage forms that you just testified as to, that you just testified about --

THE COURT: Well, all I think you have to do is to say what slide you're referring to.

Q. With respect to slide eight, Dr. Johnson, were these dosage forms available as of January 1995?

A. Yes.

THE COURT: And that's DTX-162.

MR. PARKER: Correct.

THE COURT: Go ahead.

Q. And, Dr. Johnson, with respect to the dosage forms that are listed on slide 11, were they, too, also available as of January 1995?

A. Yes.

Q. All right. Now, let's just -- we just talked a little bit about dosage forms that fall within the scope of the claims.

Did you reach any conclusions with respect to the form of atomoxetine in terms of what would fall within the scope of the claim?

A. They state that tomoxetine is a well-known drug and is regularly used as a salt, and salts are included here in the term tomoxetine to be used.

Q. Now, is there a difference between tomoxetine salt form and tomoxetine base, and, if so, can you tell us what

those differences are?
A. Tomoxetine base is an oily liquid, and tomoxetine salts would generally be a solid.
Q. Now, with respect to the potential salt forms for atomoxetine, were you able to find or locate any --
MR. BAJEFSKY: Objection, Your Honor. There's nothing in his expert report about alternative salt forms.
MR. PARKER: He never asked -- well, let me back up, Your Honor. There's a little background here.
Initially, our expert for formulation was Dr. Atul Shukla, --
THE COURT: Right.
MR. PARKER: -- who passed away.
THE COURT: Right. He adopted his report.
MR. PARKER: He adopted his report.
In Dr. Shukla's report, he mentions in his report that the claim is not limited by any form of atomoxetine. It includes all salt forms.
Now, whether or not he asked him during his deposition, I don't recall. But it's in the report.
MR. BAJEFSKY: There's no listing of salt forms. He mentions that it covers alternative salt forms. There is no suggestion that there are all these salt forms that were available anyplace in the deposition -- I'm sorry, in the expert report. There was no reason to inquire about it in

the deposition.

MR. PARKER: We cited to the '081 patent in the expert report, I believe, and that's where the salt forms were I believe identified.

MR. BAJEFSKY: But not in any way, Your Honor, that had any bearing whatsoever on the salt forms. The portions that were cited to did not deal with the salt forms, Your Honor.

THE COURT: Well, show me where in his report and/or adoption of the report that he mentions this.

MR. PARKER: Well, we do have '081.

THE COURT: Maybe the witness can do it. He might be more familiar with his report than counsel, so maybe you should ask him if he can point that out to you.

THE WITNESS: It's actually pointed out in -- the '590 patent includes atomoxetine and all salts, and that's pretty wide open. And so that to me would mean pharmaceutically acceptable salts of tomoxetine, and it's my understanding that would fall within the scope. They don't identify. Some of these products would require salts which are insoluble, and you would go to a list like this and pick out some you thought would be insoluble and try to use those. That's what I'd do.

THE COURT: I'd like to see the part of the report that refers to this, that you claim refers to this.

MR. PARKER: I'll find that in a second, Your Honor.

Just for a little more background, too, the salt forms came from another patent owned by Eli Lilly, which is the atomoxetine compound patent which we referred to, the '081 patent. Now that was attached as Exhibit 4 to Dr. Shukla's report. And I know, given a few more minutes, I will be able to find the portion.

THE COURT: Go ahead.

MR. PARKER: So let us just -- why don't we go back to this concept or this matter in a second.

BY MR. PARKER:

Q. All right. So, Dr. Johnson --

THE COURT: So we're going to another topic for the moment.

MR. PARKER: We're going to go to another topic. At some point, I have to -- I know it's around here. I want to go back and extract as opposed to doing it on the fly.

THE COURT: All right. Then until that occurs, I'll sustain the objection.

Q. Now, with respect to Wands factor three, Dr. Johnson, relative skill of those in the art, did that at all play any role in your analysis?

A. Yes.

Q. And did you yourself -- and when you were studying all

these materials and these factors, did you have an understanding as to what one skilled in the art would be?

A. On my next slide, I have -- that reflects what we tried to assess as somebody skilled in the art as of that date, and somebody that would have three to five years' experience in developing dosage, a particular dosage form; a degree in pharmacy, a B.S. degree in pharmacy or a closely related field, and the skilled formulator would have to be sophisticated enough to be able to consult with other disciplines, like analytical chemists, biopharmaceutical scientists and physicians.

Q. Now, with this particular factor, the one skilled in the art, did that have any effect on your ultimate conclusion at all?

A. Yes. Many of these are sophisticated dosage forms which I think would be very difficult for this person to prepare or develop without undue experimentation.

Q. Now, let's go on to the next factor, the amount of guidance disclosed in the patent. Did you at all consider that as part of your analysis?

A. Yes.

Q. And does the patent talk about any dosage form?

A. Yes. Column 2, 7 through 33, there is some comments about the dosage forms as we reflected on before, and the guidance reports to discuss you may dose it as tablets,

capsules, suspensions and the like, and other dosage forms which are not oral, such as sustained-release systems, injectable solutions, suppositories and the like.

Q. Now, does the patent also identify a dose?

A. Well, they give dosage ranges, but it's a little difficult to tell because they don't say -- they say it's probably a salt for this -- these capsules, but they don't say -- as I recall, they don't say that it's for a hydrochloride salt or any salt, and if you're trying to give the dose, you really need to define what the salt would be. So if you're giving -- if it's a hydrochloride salt and you say it's a hundred milligrams, that would only be about 80, 85 milligrams of base. So they really didn't define it very well.

Q. Well, do they also -- in the specification, does it tell you -- does it correlate the dose range that's identified in the patent, does it correlate that with any particular dosage form?

A. They don't say.

Q. Now, based on your review of the prior art, did you have an understanding as to where the dose ranges may have come from?

A. I assume it had to be from the -- some of the early studies on -- for depression.

Q. And how is the atomoxetine administered in those

studies?
A. It was administered in the capsule, but there's no definition of what the capsule was, other ingredients. I'm not -- I don't believe it would be -- I don't even know whether or not they set it up to atomoxetine hydrochloride.
Q. Now, with respect to the other dosage forms, the depot injections, suppositories, the injectable solutions, so there's nothing in the specification in your view that links those dosage forms with that dose range?
A. No.
Q. Now, does the patent talk about -- does the patent discuss anything about the physical characteristics of the compound atomoxetine?
A. There's very little description about the compound. It just sort of defines what it is.
Q. Can you tell us where the patent is located?
A. It's line 54 to 59, and in column 2, lines 1 to 3.
Q. And so when you refer to lines 54 to 59, were you referring to column 1?
A. Yes.
Q. All right. And what's discussed there?
A. It just states that "Tomoxetine is a well-known drug, the chemical name is -- it's phenylpropylamine. And "It is regularly used as a salt, and salts are included in the term tomoxetine as used here." Again, they really don't define

which salt is used here in this patent.
Q. So now with respect to discussing the dose form, the dose, and the physical characteristics of the drug itself, is what's up on your slide, is that about the extent of what the patent states in connection with that subject matter?
A. With regard to formulation, they're trying to determine what kind of -- how to make something, yes.
Q. And did you come to any conclusions with respect to that disclosure in the specification in terms of your analysis?
A. Yes, I thought it would make it difficult for someone to do this without undue experimentation.
THE COURT: You found it difficult to do without experimentation?
THE WITNESS: Undue experimentation.
THE COURT: Undue experimentation.
Q. Now, the claims also use the phrase "effective amount." Do you recall that?
A. Yes.
Q. Now, is there anything in the specification -- when you review the specification, did you see anything indicating as to what would constitute an effective amount for any particular dosage form?
A. They don't -- they don't relate the effective amount that they proscribe to any dosage form.

Q. Now, if you move to the fifth Wands factor, the presence or absence of working examples in the patent, did you consider that factor in your analysis?

A. Yes.

Q. Now, in your review of the patent, did you come to any conclusions as it relates to this particular factor?

A. Yes. There are no working examples in the '590 patent.

Q. Now, working examples, what does that -- what did you believe that to mean?

A. It means to me that you like to see a starting point, you like to see -- if they're treating somebody, you really need to know a close or an approximate dose -- you need to know, you'd like to see some working examples of how you make the dosage form that they claim would be useful to use. You'd like to see some ranges. You'd like to see some tests run on the product, in other words, either stability or dissolution rates, and these are commonly used.

Q. And was any of that information in the specification?

A. No.

Q. Now, how did the fact that there existed -- that the '590 patent disclosed no working examples, what effect did that have, if any, on your analysis?

A. It means that you have to start very early in the process and would favor undue experimentation.

Q. Okay. Now, let's go with the last three Wands factors, which maybe will take some time. This is the predictability of the art, the quantity of experimentation necessary, and the state of the prior art.

Dr. Johnson, we're going to take these all together. Is that okay with you?

A. Fine.

Q. Probably be a lot faster; right?

A. We hope so.

(Laughter)

Q. Okay. Now, how did you look at these factors when you were -- in your analysis? How did you implement these factors in your analysis?

A. I looked at them in the context of the last 40 years. After taking a look at these dosage forms to see how predictable is it, how long would it take, what's the state of the prior art, do I have to reinvent the wheel, is anything there to help me, and I try to just ascertain whether or not -- what it's going to take to do these things.

Q. Now, let's just talk a little bit, just briefly, you have -- with respect to immediate-release capsules and tablets containing atomoxetine hydrochloride, did you reach an opinion as to whether or not it would require undue experimentation?

A. Yes.
Q. And what was your opinion?
A. I decided that you could probably say or you could -- you could say that the immediate-release capsule tablet would be stable containing atomoxetine hydrochloride.
Q. Can you just tell us in general what's the basis of your opinion in that regard?
A. Well, we go back -- we went back to some of the prior art, and there were capsules and tablet formulations listed which in my experience I believe would work. It's a dry system. There's no -- there's no -- going to be little or no moisture there. So it's most likely that it would be fairly stable.
Q. Now, let's go through the -- can you tell us what's on the right-hand side?
A. Yes. On the right side, these are a representative list of dosage forms that I thought would -- I would consider nonenabled, like depot injections, transdermal patches, suppositories, suspensions, injectable solutions, sustained release formulations, and a variety of others.
Q. And in reaching that conclusion, and we'll over go over that in detail, did you consider the quantity of experimentation?
A. Yes.
Q. And the predictability?

A. Correct.
Q. And you also considered the prior art as well?
A. Correct.
Q. All right. Why don't we just start off with depot injections?
Now, this was a slide that was prepared pursuant to your direction, was it not, slide 22?
A. Pardon me?
Q. This was a slide prepared based on your supervision and direction; correct?
A. Right. I dictated the process.
Q. All right. And does this slide, Dr. Johnson, accurately reflect, again, based on your knowledge and experience, the steps one skilled in the art would undertake to prepare a depot injection?
A. Yes.
Q. Can you please explain, what is a depot injection?
A. A depot injection is where you put the drug in some sort of matrix and inject it, either under the skin or in the muscle, typically.
Q. What's the purpose of a depot injection?
A. You do it so that you can just dose periodically, you don't have to dose every day, or if it has a five-hour half-life you don't have to dose twice a day, or -- like that. So you can maybe give weekly injections or injections

that might last a month or up to six months.
Q. Are there any depot injections on the market today that you're aware of?
A. I have a list, but I didn't count them, but I think there's on the order of 25 or so. Some are veterinarian, and a number of these are human.
Q. But again, can you give a specific example of any depot injections on the market today?
A. One that we've looked at was Maltrexel (ph). In fact, we had the NIH grant for Maltrexel depot injection, and we could sustain it on the order of two weeks to a month, but I don't think our technique was suitable. It was also a product, the Maltrexel injection, and Alchemy (ph) designed it, and I know it took them well over five years.
Q. Now, I believe you used the phrase, at least maybe during the deposition, but viable dosage form. Does that sound familiar to you?
A. Yes.
Q. And what is a viable dosage form?
A. I use it as a -- in the context of a dosage form sufficiently refined so that I'm willing to put it in people.
Q. So let's just back up. How does that relate at all to your analysis? And if you can put it in context of the schematic with depot injection. How does that play into

your analysis?

A. Well, we -- you just don't put it in a glob of wax and inject it. You really have to -- you really have to do sufficient preformulation, formulation work and safety work to know that you can put it into people with a high degree of safety.

Q. Now, but with respect to the formulation steps that you've laid out in slide 22 and 23, is the end result the preparation of a viable dosage form?

A. Yes. It's something that --

Q. Now, in these schematics, we're not talking about a dosage form approved by the FDA for commercial sale; correct?

A. No. No.

Q. Would a viable dosage form be one that would enable someone to -- would enable a physician to practice the claimed invention?

A. Yes.

Q. And we'll get into how, where that step fits into the process.

Now, can you please explain to the Court the process that a person of ordinary skill as of January 11th, 1995 would have followed in preparing a depot injection comprising an effective amount of atomoxetine for the treatment of ADHD?

A. Yes.
Q. Please do.
A. On our slide, we put a number of the steps that we would do. I've done two columns. On the right side, on the right side, I just used the base, because it's possible we could do this with the base. Another side would most likely have to do inside the salt. So that would be -- either one of these would require a certain amount of work to try to characterize them and purify the raw material and develop that so we're in a position we could actually develop these products.
Q. All right. So let me just -- where were you? Were you on -- with your pointer, can you point us to where you are on this process?
A. Well, right at the top, so -- what I was going to do is maybe briefly I can go through one of these, and then if you want, you can ask me questions to clarify it, or I'll do it --
Q. No, no, I just mean with the selection.
MR. BAJEFSKY: Your Honor, can we have the question-answer format rather than a narrative answer so I can object, if necessary?
THE COURT: Yes, you can certainly -- we need a question-and answer-form. But sometimes the response is an explanation. I thought you were asking him about the

process --

MR. PARKER: Yes.

THE COURT: -- or how he did something.

Well, I don't know how he answers that other than to go through it. It seems to me to make an amount of sense.

A. Okay. So I'll just briefly go through the process to show what we're talking about and then answer your question.

Q. Well, before you do that, Dr. Johnson, is there any information in the prior art that atomoxetine can be used in a depot injection?

A. No.

Q. So having the '590 patent in hand, why would someone have to go through all these steps?

A. Because there's no information to help.

Q. And there's nothing in the prior art, to your knowledge?

A. Not that I'm aware of.

Q. So why don't we begin with selecting a form of atomoxetine?

A. I'm aware that you can also take a base like this and put it in certain solvents, and the base, what we're going to do is, we're going to purify the base. We will put it in some sort of -- disperse it in some sort of system, and then we would need to look at the purity, stability,

compatibility and solubility in this vehicle. And if we want to take this and try to see whether it would be sufficiently long, in other words, if we dose it once a week, it might work, we can put it in a hydrotropic system, solution, after we understood that it might be stable in that system, and then we would develop a variety of these solutions, we would do dissolution on the systems as well as stability, and once we got a system we thought was -- would work, we would go to the next page.

Q. Okay. So, again, so you've already talked about the -- you're over here. We're talking about selecting the form of atomoxetine, and you just described selecting the -- using the base as a potential --

A. Right. I'm trying to just go down the simplest system that I can think of.

Q. Okay.

THE COURT: Well, if this is the simple system --

(Laughter)

THE COURT: Because I'm confused. You're telling us now the way you would go about this?

THE WITNESS: Your Honor, I'm telling you about -- this is the way we did go about it.

THE COURT: Okay.

Q. Well, Dr. Johnson, would this be a way that one of ordinary skill in the art would have gone about it in your

opinion in 1995 if they had to --

A. He would have gone through most of the same steps, I believe.

Q. Okay. Now, with respect to the compatibility, stability, purity, --

A. Right.

Q. -- okay, and what's the purpose of conducting this type of testing?

A. We want to characterize the raw material to know what the solubility and stability are so we know what other things we could mix with it. We would typically take the base and mix it with a variety of solvents and determine if it was stable.

Q. And why does one skilled in the art need to conduct crystal purity testing?

A. Well, in this case, we won't have a crystal, but we still have to make sure that our oil in this case, which we believe it would be, would be pure.

Q. And how does one skilled in the art go about conducting this type of testing?

A. You typically would find ways to make sure that the -- you use mass spec or some other way, carbon hydrogen analysis, nitrogen analysis to make sure that you're getting close to 100-percent pure, you don't have the composition product.

Q. Why does one skilled in the art conduct stability testing?

A. Because you can't give people unstable product.

Q. And how does one go about conducting stability testing?

A. Usually you put the form that you want tested at elevated conditions and you subject it with oxygen or light, heat, and analyze it after periodic intervals.

Q. And now, again, for compatibility testing, why would someone want to carry on compatibility testing?

A. Because sooner or later you're going to have to mix it with something to dose it, so you want to have -- determine what range of materials you might want to work with.

Q. Now, you have a number of arrows -- and I'm referring to slide 22 -- you have a number of arrows that are associated with the blue diamonds up top: Solubility, compatibility and stability and purity testing. Do you see that?

A. Yes.

Q. What were you trying to illustrate with those arrows?

A. That many of these steps are iterative, and you hope you guess right, but typically, you don't.

Q. And how many cycles -- based on your experience, how many cycles would you expect?

A. In the top row, you would probably have at least one

cycle, going from preliminary formulation, in vitro dissolution testing, you might have many cycles. Most likely, you would have more than two.

Q. Now, would you consider these an aspect of -- with respect to this aspect of the process, development process, would you consider any of that routine?

A. No.

Q. Why not?

A. Well, most of the decisions are going to be complex. Some of the mechanics of let's say putting oil in a beaker or something like this is not complex, but the interpretation certainly is.

Q. Now, could a person of ordinary skill in the art predict without conducting any solubility, stability, compatibility and purity tests whether or not the base would be suitable for depot injection?

A. No.

Q. Nothing in the literature that would help you, would help one skilled in the art? Is there anything in the literature?

A. There are a few things that might actually help you, but not -- you would still have to do the work.

Q. Now, based on your experience, how long do you believe it would take one skilled in the art just to carry out and conduct that first aspect of the development process?

A. What's the first aspect?
Q. Well, the one we're talking about, the solubility, compatibility, stability, and purity testing.
A. That's probably three to six months.
THE COURT: Three to six months?
THE WITNESS: Correct.
Q. Now, can you explain, with respect to selecting the form of atomoxetine, is also a choice that one skilled in the art would have, and that's dealing with insoluble salt selection; right?
A. Yes.
Q. And why does it have to be insoluble?
A. Because atomoxetine hydrochloride is too soluble. You really wouldn't be able to sustain release of that for any length of time. With Maltrexel, they made a stearate salt, and that's one of the things that helped them. In addition to making the stearate salt, they encapsulated it.
Q. So atomoxetine hydrochloride, that would -- in your view that would not be an appropriate salt form?
A. No. It wouldn't work.
Q. Now, over here, you also have listed solubility, compatibility, stability --
A. We've actually tried Maltrexel hydrochloride, and it really didn't -- you couldn't sustain it for any length of time.

Q. And that was actually a depot injection?
A. Yes.
Q. Now, over here in the process, you have solubility, compatibility, stability, and crystal purity testing. Do you see that?
A. Yes.
Q. Now, is that the same level of -- with respect to the quantity of experimentation that you described in connection with the base with those same tests, is it the same for the insoluble salt selection?
A. It would probably be more, because you would most likely select two -- try to make at least two or three different salts. So you'd be doing this three times, I mean, in parallel, but you'd be doing it with multiple salts.
Q. So over here when you have the arrows in the yes and noes that are indicated on slide 22 up there by the purple diamond solubility, compatibility, stability and purity, what were you trying to convey there?
A. That -- two things, actually. I probably would have three more boxes for the different salts, but most of the time you're not going to be able to guess at the solubility, so you have to do the work. You might have to go back and do it over again and choose different salts.
Q. So one of ordinary skill in the art would not be able

to predict an appropriate insoluble salt form without conducting these tests. Is that your opinion?

A. That's my opinion.

Q. And how long would it take one of ordinary skill in the art in your view to complete this phase of the development?

A. I would think that would maybe take more than -- more than six months.

Q. Now, once you've selected a potential insoluble salt form of atomoxetine, what is the next step one skilled in the art would conduct?

A. We would -- we would try to put in a system suitable for injection.

Q. Can you just -- is this where --

A. That would be our preliminary formulation stage.

Q. So it would be a preliminary formulation and excipient selection?

A. Right.

Q. Now, underneath, you have four boxes and it says microparticles, rods --

A. Right.

Q. -- the AQ, -- which is aqueous -- suspensions?

A. Right.

Q. -- and oil suspensions?

A. Right.

Q. Can you tell us what those are?
A. Those are just some examples of different systems that you might choose to do this. I think what we followed through with here was the aqueous suspensions because that's been used for many years and it's a common system.
Q. So now what would one of ordinary skill in the art do at this point in the development process?
A. You would try to -- try to make this insoluble salt a suitable particle size and a formulation good enough so that it wouldn't settle so fast that you can't inject it. You would do -- probably choose multiple particle sizes because in this system, that's really going to control your rate of dissolution, and you look at the stability and you try to get this in sufficient state that you could do the dissolution steps with predictability and consistency.
Q. Okay. Now, you also mentioned settling tests. What does that -- why does one need to carry out --
A. If it's a suspension and you're drawing it out of a vial, it's got to stay in suspension long enough without settling so you can actually get an accurate dose.
Q. And how would one go about carrying out a settling test?
A. Well, there are many ways that you can do it. You can do it -- actually, the easiest way to do it is just take vials and take multiple doses out of the vial periodically.

That's probably the easiest way to do it.
Q. And just tell me, why would one of ordinary skill in the art carry out the particle size test and stability test?
A. The particle size is pretty important in this model so that you can adjust the solution rate of the drug in the depot injection into the body so that we can control how fast it's going to dissolve and go into the body.
Q. Now, again, you have arrows and you have the yes and noes going up and down. What were you intending to convey there?
A. That you probably will have to repeat this multiple times.
Q. Now, based on your experience -- well, could one of ordinary skill in the art predict the outcome of these tests?
A. No.
Q. They would have to carry them out?
A. Yes.
Q. Now, would you consider these tests, the particle size test, the settling test and stability test to be routine in connection with the development of a depot injection at this stage?
A. Well, the mechanics of weighing and measuring are not -- not difficult, but interpretation certainly will be.
Q. Now, what do you mean by the interpretation?

Interpretation of what? The data?
A. Well, yes, and you're going to -- from all these experiments, you always get data, get data, get data. And what do I do with it? Can I make sense out of it? Can I put the pieces together and actually proceed forward? So that's always the hard part, always.
Q. And making judgment calls based on the data, would that be something that you would consider difficult?
A. Yes.
Q. And how long would it take for one of ordinary skill in the art in your opinion to carry out this stage of the development?
A. Maybe another three to six months. I mean, try to -- all this stuff, maybe you try to -- could do it in less than a year. If I was, I'd probably be lucky.
Q. Excuse me?
A. I'd try to do it in less than a year, but it's going to be one plus or minus.
Q. Now, again, there's no information out there in the prior art that would be able to deal specifically with atomoxetine in connection with depot injection; right?
A. Not specifically with atomoxetine.
Q. Now, with stability testing, you mentioned, just so we can kind of move along, you mentioned that you would look at the -- I guess the interaction of the formulation in

connection with heat, light, and oxygen?
A. Right.
Q. Would that be the same here as well?
A. Yes. Yes.
Q. Now, with respect to the quantity of experimentation that you just described with the insoluble salt here, would that be relatively the same for the base?
A. It would probably be -- probably be more.
Q. More? Why is that?
A. You mean at that point or --
Q. At this point over here. I'm showing you the particle size test, and the corresponding test of solubility --
A. They'd be similar.
Q. They'd be similar?
A. Similar.
Q. And the same with respect to predictability: Would that be the same, would they be the same, roughly?
A. They'd be equally unpredictable.
Q. And again, as far as the prior art, there's -- any information in the prior art with respect to atomoxetine base and how it would react in a depot injection?
A. No.
Q. And in terms of time, how long would it take one of ordinary skill in the art to complete this aspect of the development process?

A. Another three months plus. It's very difficult to get these correlations of how fast it's going to dissolve in some of these in vitro tests, and there aren't very many in vitro tests. We're actually trying to develop a mechanistic study of prediction. We have rat data and we have dissolution data on these hydrophobic vehicles with bases where we're starting to get some predictions. So in the future, we're going to be able to do this quite a bit faster. But at the time, we can't find anybody else who's done it.

Q. But as of 1995 --

A. No. No.

Q. -- these types of tests weren't available.

A. No.

Q. Okay. Now, we did not go through, and I just want to see if we can go through this real quickly, we didn't go through microparticles, rods and oral suspensions in connection with the insoluble salt, but would your testimony be the same with respect to quantity of experimentation at this portion of the development stage where you're leading into the in vitro solution, multiple samples?

A. Yes, except that the preliminary formulation would be expanded. That would be more difficult.

Q. In connection with microparticles?

A. Yes.

Q. What about, would it be the same for rods?
A. I believe so.
Q. And oil suspensions?
A. I believe so.
Q. And also, if you look to the base selection, you have microparticles, rods, would that also be the same in terms of the quantity of experimentation as you described it in connection with the aqueous suspension?
A. Yes.
Q. So what's next for one of ordinary skill in the art? Once they've conducted these tests, and I guess they've been able to get something that's of a potential preliminary formulation and excipient selection -- and before I begin, what is an excipient?
A. It's an ingredient that we utilize in conjunction with the active ingredient to make a dosage form.
Q. So is an excipient everything inside the pill, the capsule?
A. It's everything else.
Q. Other than the active ingredient.
A. Right.
Q. And you say compatibility with excipients. What are you referring to?
A. Well, you know, if it has an effect on pH, it may cause it to precipitate; does it react with the drug.

Mostly things like that.

Q. So you look at whether or not the active ingredient is -- if the active ingredient is incompatible with the particular excipient, can you give us an example of what could happen?

A. It would probably -- usually what you see in some of these systems, certainly in sustained-release systems, if you -- if you form a eutectic mixture, for example, it will change the melting point. That's especially the problem with suppositories or something like that.

Q. Okay. All right. Now, let's go to the -- again, with the steps we were referring to, this is the particle size, settling test, stability test, and over here, stability test, solubility test, now, where are we going and tell us where is it that -- based on this schematic, where is it that one skilled in the art -- what does one skilled in the art have to do next?

A. We refine the formulation so it would be suitable for injection into an animal.

Q. Okay. So we're now from the in vitro dissolution, multiple samples, we're now down to refining the formulation?

A. Right. Right.

Q. Now, why are we refining the formulation? Why would one of ordinary skill in the art refine the formulation?

A. We're going to have to refine it in terms of dose per unit that we can actually inject or utilize to determine whether or not it has activity.

Q. Okay. Well, let me just back up.

What do you mean by refine formulation?

A. Well, we'll modify it. In other words, we made the solutions, stability at one percent or .5 percent. Now we have to put a set amount of drug in a set amount of liquid, in this case let's say, so we can actually dose it to an animal.

Q. Okay.

A. So you have to refine it so you get the right amount, and like with a rat, I can inject maybe half a ml or less. So I have to put the dose that I'm looking for in that quantity.

Q. So now focusing on the refined formulation aspect of the development, you have identified five tests: Syringeability, stability, in vitro dissolutions, sterility, and injection site. Do you see that?

A. Yes.

Q. Now, syringeability, what is that? What does that mean?

A. Well, we injected these from a syringe, so it has to be able to pass through the needle and into the site where we're injecting it.

Q. And how would one skilled in the art go about doing that?

A. You may do it very simply by just picking up the liquid and pushing it out, and if it doesn't take a lot of -- a lot of strength, you might do something as simple as that. Otherwise, we have a device where we can -- we can calculate the pressure needed to expel the liquid over a period of time.

Q. Now, what about stability testing? Is that the same as you've discussed before -- Dr. Johnson, we have to make sure -- when I finish, then you can begin.

With respect to stability testing, would you just describe what type of tests those would entail?

A. Could you repeat the question?

Q. Stability testing; what does that entail?

A. What it would typically do for stability testing now that we have changed the ingredients, we would confirm that our stability assessments that were made in this first stage are still -- still firm and correct.

Q. And in vitro dissolution testing?

A. Yes. We would repeat the in vitro dissolution at the concentrations that we were actually going to utilize for injection.

Q. And why would you have to repeat them?

A. Well, these tests at this point really aren't

predictive enough that we can tell, so we would do that again.

Q. Now, what is sterility? What do you mean?

A. We have to make sure it's sterile. If it's a solution, we can push it through .2 mic or a small filter and that will probably be adequate as long as we prepare the sample under sterile conditions. If it's a particle size, let's say particulate matter is much more difficult. We may radiate it or we may make sure that this -- we'll prepare the powder sterilely and then we'll aseptically fill and put the product together.

Q. Now, you have over there identified injection site. What do you mean by -- can you just explain what you mean by that?

A. What we want to evaluate is the injection site after injection to determine whether or not we have any untoward reactions to our drug, our vehicle, our system.

Q. And how would you go about testing that?

A. Usually we'll inject placebo vehicle, and we will examine the site daily and we'll probably biopsy it at one, three, five, seven days, depending on the length of time or duration of injection that we think would be used.

Q. Now, you have again a series of arrows, yes and noes. What is it that you were trying to convey there?

A. We're just simply trying to convey that many of these

steps are iterative. We don't always guess right.

Q. Now, do you have an understanding or at least do you have an opinion as to how long it would take one of ordinary skill in the art to carry out these series of tests in order to begin any animal studies?

A. With some of these, with the base, we probably can do this fairly quickly, like less than three months. With some of these particulate matter, we've done it with insoluble salt, I think it's considerably more difficult, so it's probably more than that.

Q. And why would a salt be more difficult?

A. Well, you've gone to a particle, and this particle is controlling your dissolution rate for the most part, and the coating, that's an additional complex factor.

Q. And the particle size also, I believe you mentioned, has an effect on sterility?

A. Well, it's -- it's more difficult to actually prepare sterile powders than it is to sterilize the solution.

Q. Now, at this point, is there any indication whether or not the base would be appropriate for depot injection, would you know?

A. We have a decent idea of whether -- but it really all depends on what kind of extent or magnitude of duration of action we're trying to get. If the outline of the project we're trying to do is going to be let's say two weeks to a

month, well, let's say more than two weeks, up to a month, it's not likely that the base -- we're going to be able to do that. That's not likely.

Q. Now, could a person of ordinary skill in the art predict without conducting any of these tests whether or not a particular salt form of the atomoxetine or the base form would be suitable for the animal studies that you identified in your next step?

A. No.

Q. You'd have to conduct these tests; right?

A. Correct.

Q. Is there anything in the literature that would assist one skilled in the art to make this prediction that you're aware of?

A. Not with atomoxetine hydrochloride, or its salts.

Q. All right. So now that you've refined the formula, so what is the next step one of ordinary skill in the art would have to conduct?

A. In my assessment, you'd have to take this to animal PK studies and determine whether or not it would be safe to go to humans. And we'd be very interested in trying to determine the relationship of any blood level we achieved with our dose.

Q. Now, you mentioned before you had -- I'm sorry, can you repeat? So in order to confirm that it would be safe to

go into humans? Can you repeat that?

A. Yes. Our goal is to try to exercise this claim one, and to do that, we have to do a human efficacy study. The problem is, we don't know the dose, we don't know the safety. So we -- and in my discussions with people from the pharmaceutics group at FDA, they suggest that we do -- have to at least do dogs and probably rats, and they thought I would have to do monkeys. And we've done dogs and rats and mice, but we haven't done the monkeys yet.

Q. All right. Well, let's just go back, and let's focus a little bit on the animal PK studies.

What animal would you use in testing?

A. We'd start with rats because it's easy, you can do it fast, and it's a reasonable in vitro model.

Q. And approximately how long would it take to conduct these studies?

A. You'd probably have to do at least two or three -- you'd probably do multiple stages, because what we don't know now would be the effect of a single-dose study, multiple-dose studies, or injection site location. So we would probably repeat these, and these would be -- we'd probably work -- and my plan as I recall was about a year, nine months to a year.

Q. Just to do the animal PK studies?

A. Right. Right.

Q. Now, you used the word "PK." What does PK stand for?
A. Pharmacokinetic.
Q. And what is it that you're --
A. Well, we try to determine the parameters of excretion, absorption, and dissolution from or at least partitioning from our dosage form into the bloodstream so we have an idea of relationship of dose versus blood level that we would achieve.
Q. Are you also getting a relation with respect to release?
A. Yes.
Q. Now, how would one measure -- I mean, what kind of analysis would one have to carry out to determine the release? I mean --
A. Typically, we would do it -- we would do a blood level study first with an injectable solution, so we would get the purer, let's call them, pharmacokinetic parameters, and then we would start injecting our dosage form at probably at least two doses.
Q. Okay. As to now when you say -- I just want to get into the how. So how? You inject rats, you extract blood?
A. Right.
Q. What does the analysis entail?
A. We analyze it with an LCMS device, an analytical technique.

Q. That's going to require a development standard, is it not?

A. You have to do standards. You have to do -- you have to develop an analytical method. That's -- and then in this case, it's probably a two- to four-week to three-month job.

Q. To develop the analytical test --

A. For the plasma, depending on the level -- level that you're studying. If it's very low levels, it takes longer.

Q. I just want to be clear. You mentioned as far as carrying out the analytics, you have to develop the analytical test methodology; correct?

A. Correct.

Q. And that would take some time?

A. Yes.

Q. And how long do you think that would take?

A. One to three months.

Q. Okay. Now, you also mentioned irritation. So why is that a test that's carried out?

A. If it's irritating at the injection site, you may be dead in the water quick.

Q. And so how is that test carried out?

A. We will biopsy the site. We'll look at the surface and see whether or not it's puffy, red, mounded, and we'll biopsy it and prepare slides, go to a pathologist, and he'll look at them.

Q. Now, at this point, if I -- again, you have a circular arrow next to the animal PK studies and irritation stage. I'm referring to slide 23. What does this indicate?

A. Iterative steps.

Q. And any idea, in your own experience, how many cycles that may go through or could go through?

A. It could be many. We've gone through many with buphenophrine where we have gone through many iterations and variety of concentrations. We've gone through a variety of dose levels. It's --

Q. Now, what comes next? Okay? After you -- you've made a refined formulation, now, you've carried out a series of animal PK studies and irritation studies. So what's the next step for one of ordinary skill in the art?

A. We would want to do human PK studies to get a relationship of the dose we would want to try with people.

Q. Why would you have to carry out human PK studies?

A. Because we don't know the dose.

Q. Well, what information, what data would you need to extract from these studies?

A. We would try to get a relationship between the blood level and the injection amount.

Q. Particle size of the compound, would that also be --

A. It would -- we would hope we would have refined it sufficiently by this time we don't have to keep repeating

it, but that would -- for an insoluble salt, that would be an issue.

Q. Okay. Now, these human PK studies, these are not individuals that have ADHD; right?

A. No, these are -- this is --

Q. Healthy volunteers?

A. Yes.

Q. How many patients would be necessary to carry out these studies, to sufficiently carry out these studies?

A. You'd probably do a pilot study of four to six people, and then to get really good results, you'd probably need at least a dozen.

Q. So you have to go from four to six people, get some results --

A. Well, you'd work out your technique and everything. You'd want to do a pilot study with this. It's a new dosage form, it's not -- not routine.

Q. Right. So in fact, let me ask you this, then. With respect to the animal PK studies and the irritation studies, would you consider those tests to be routine?

A. No.

Q. Why not?

A. They're very, very difficult and sophisticated in interpretation.

Q. What about it makes it difficult?

A. Interpretation of the data.
Q. Okay. So what is it about the data that one skilled in the art would find challenging in interpreting?
A. To try to relate the release of the drug back to the blood level. There's so many things that happen, it just doesn't seem to be real simple. It's not always straightforward.
Q. Can you give us an example of some of the things that could happen?
A. When you inject these, you may have injected not consistently in the right site. In other words, you -- the technician may have rubbed the site. So many things happen that -- it makes a difference.
Q. All right. Now, again, with respect to these studies on slide 23, and I'm referring to the purple diamonds, okay, up top, would you consider these tests individually as routine?
A. Syringeability probably would be. Sterility -- we would -- no. Injection site, no. Generally, they're not.
Q. Okay, but you said syringeability would --
A. Yes, we could train somebody to do that fairly simply.
Q. But your opinion is not the same with respect to the other tests identified in the blue diamonds -- I'm sorry, purple diamonds.
A. In my experience, that is not the case.

Q. And we're referring to one -- and again, when you're giving -- your opinion is with respect to one of ordinary skill in the art; correct?

A. Correct.

Q. So now you've carried out the human PK studies.

Did I ask how long would that take to carry out the human PK studies?

A. I think you could probably do that in less than six months.

Q. Less than six months. Approximately, can you give me an approximation? More than three, four, five?

A. Well, you're not going to do it in less than three months. You can maybe complete it in six.

Q. Now, obviously, you're a formulator.

A. Right.

Q. Who would carry out the human PK studies?

A. We'd go to a biopharmaceutics lab. We have a fellow on campus who has done literally hundreds of tests like this.

Q. Okay. So once those tests are carried out, and -- well, let me ask you this. Before you even get into human efficacy studies, and we're going to talk about that in a second, approximately how much would this cost to go from -- hold on -- to go from selecting the form of atomoxetine to complete the human PK studies on slide 23, about how much

would that cost? Approximately.
A. It's millions of dollars. Alchemy spent I believe tens of millions of dollars.
Q. This is how -- I'm now asking about the cost as you would see it as of 1995, January 1995. Is that about -- would that be millions of dollars?
A. Well, roughly. It's just that -- it's my understanding they kept repeating the human PK study because it was very difficult to get it consistent and reproducible.
Q. So let me just ask you, so in your view, based on your 40 years of experience, okay, how much do you think it would cost around as of 1995 to conduct all the tests from the selection of the atomoxetine form to complete human PK studies?
MR. BAJEFSKY: Objection, Your Honor. There's nothing about cost in his expert report.
THE COURT: Well, I have a little, other difficulty.
First of all, do you feel comfortable making a guesstimate as to what it would cost back in 1995?
THE WITNESS: It's difficult.
THE COURT: Okay. Even if it's difficult, would you feel comfortable, do you think you can make in any kind of way an accurate assessment?
THE WITNESS: It's not -- it's not less than a

million, and it's -- from our scheme here, which is rather simple, it's I'm sure less than 10. So two to five.

THE COURT: Well, now I've heard not less than a million, two to five, and 10.

THE WITNESS: I'm trying to narrow it.

THE COURT: I know. Because it seems to me that this verges on the impossible to try to make a legitimate estimate of this.

So whether it's relevant or not relevant, I'm having trouble with giving it much credibility.

MR. PARKER: Well, let me just see if I can --

Q. Dr. Johnson, in your experiences, as part of your responsibilities at Schering-Plough, did you have to advise the company as to --

THE COURT: One of my problems here is trying to put this into 1995 dollars.

MR. PARKER: Right.

THE COURT: And you know, even though -- I don't know how we do this.

Why don't we go on to another subject?

MR. PARKER: Okay.

THE COURT: In the couple of minutes that we have left.

BY MR. PARKER:

Q. Okay. Now, Dr. Johnson, now that we've gone through

human PK studies, what is the next step one with ordinary skill in the art would have to undertake?

A. We would have to do a human efficacy study.

Q. And why is that?

A. Because in the exercise of the practice of the '590 invention, you have to show human efficacy.

Q. What is it about the claim that says you have to show or have human efficacy?

A. It's for treating ADHD and administering atomoxetine.

Q. Does the claim recite the word, the phrase "effective amount"?

A. Yes.

Q. Does that have any -- does that also relate to whether or not you would have to conduct human efficacy studies?

A. I think so.

Q. So, again, now, is it your goal in -- with respect to this schematic, this -- in terms of developing a depot injection, is it your -- are you describing the process in which you would actually end up with a product that would be approved by the FDA for commercial marketing?

A. No. What we're trying to get here is a dosage form which would treat a small number of people for four to six weeks to determine whether or not this dosage form would have efficacy.

Q. And how long do you think it would take, based on your

experience, how long do you think it would take to have these studies carried out, human efficacy studies?

A. Probably six months or more.

Q. Now, in human PK studies, you also have an indication, you have a rounded circle. What is that related to, mean?

A. That means that you might have to repeat these studies with a modified dosage form.

Q. In your experience, when developing a depot injection, what are some of the challenges that one would encounter?

A. Starting from the beginning or the end? I mean, in the first place, you really have to find something that's going to release the drug in sort of the manner and rate that you think would be acceptable for the period of time you've selected, so you try to decide, is this a seven-day dosage form, is it a one-month dosage form. That goes to determining which technique am I going to try to determine is useful for making one of these dosage forms.

Q. What about the term dose dumping?

A. That's what you've got to be very careful with. Any sustained-release dosage form, even if it's just a simple oral dosage form, if the dose dumps, that can cause toxicity problems. Now, with the sustained release, if you have a one-month dose that dumps for some reason or other, it could kill someone. So it's not -- not reasonable to take dosage forms that aren't really thoroughly tested into a clinic and

determine whether or not it's going to -- going to work and show efficacy.

Q. Now, is dose dumping a challenge that one would have to deal with in development?

A. That's one of the big challenges.

Q. Now, based on your consideration of the Wands factors, have you formed an opinion as to whether as of January 11th, 1995, undue experimentation would have been required by a person of ordinary skill in the art to prepare a depot injection in an effective amount of atomoxetine to treat ADHD?

A. I would think it would cause undue experimentation.

Q. Now, you know that --

MR. PARKER: Well, Your Honor, I can -- just a couple minutes or, do you want to go to exactly three?

THE COURT: I don't want to go later.

(Laughter)

BY MR. PARKER:

Q. Dr. Johnson, you are aware that Plaintiff has retained a formulator expert, Dr. McGinity?

A. Yes.

Q. And did you read his deposition testimony?

A. Yes.

Q. Okay. Well, let me ask you this question. Could someone simply take sesame seed oil, take atomoxetine

hydrochloride, put it all together and just use that as a depot injection?

Let me go one step further. Let's assume hypothetically you had a tablet, and you knew the tablet had 60 milligrams of atomoxetine hydrochloride, and you knew that tablet was effective for treating ADHD. Could you simply grind that tablet up put it in sesame oil and call that a depot injection?

A. I'd be afraid to do that.

Q. Would you put that in your child?

A. No. Do you think a pharmacist -- do you believe that a physician would actually ask a pharmacist to compound a depot injection for treatment of ADHD in a child or an adult?

A. I don't believe he would.

Q. Are you familiar with the treatises, Remington and Ancill (ph) and --

A. Lockman (ph).

Q. Oh, Lockman. Are you familiar with those treatises?

A. Yes.

Q. Could one of ordinary skill simply look to these treatises and be able to find a nice recipe and be able to develop a depot injection of atomoxetine to treat ADHD?

A. You could use these for starting points, but they wouldn't really provide very much help.

Q. And would your opinion change one way or the other as to the level of undue experimentation that would be necessary?

A. No. In fact, we did use Lockman, I believe, in that. I believe we have used these in the past as references and starting points.

MR. PARKER: This would be a good point to stop, Your Honor.

THE COURT: All right.

All right. Well, we will resume, then, on Monday.

Now, I have a problem on Monday morning. What are we doing? A sentence?

We're going to start at 10 o'clock Monday morning.

Believe it or not, I have lots of other things going on.

(Laughter)

THE COURT: Next week, perhaps, there are a couple of days we might go a little later than four to try to make up some of the time. So why don't we see where we're going?

And other than that, we'll see everybody here at 10 o'clock on Monday morning.

Enjoy your weekend.

(Matter adjourned until Monday, May 24, 2010, commencing at 10 a.m.)

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